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THE GENESIS OF HEART SOUNDS

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IT IS possible that the existence of the heart sounds was known to Hippocrates[1] and even that he made use of his knowledge for diagnostic purposes, but William Harvey[2] seems to have been the first to make specific reference to them: "With each movement of the heart as a quantity of blood is delivered from the veins to the arteries, a pulse takes place, which may be heard in the chest."

It is rather astonishing that the physicians of that time had thus far paid no attention to the heart sounds, but it is even more astonishing that their existence, when pointed out by Harvey, was soon denied. It was Parisanus[3] who said, "Neither we, poor deafs nor any other doctor in Venice can hear them, but happy he is who can hear them in London."

Although Harvey placed beyond doubt the existence of sounds accompanying the heart's activity, Läennec,[4] nearly two centuries later, gave the first precise description of the character of the sounds in normal and pathologic conditions and founded the art of auscultation.

Once the existence of the heart sounds was established, their cause was sought, and thus began an interminable series of investigations, controversies and theories, which have not ceased even at the present time. Theories on the causes of the heart sounds multiplied at such a rate that in 1881 Sandborg[5] collected no less than forty, most of which were entirely without clinical or experimental basis and often revealed a complete ignorance of cardiac physiology on the part of their originators.

The first serious attempts to elucidate the exact causes of the heart sounds were made from 1835 on by various committees appointed by the British Association for the Advancement of Science.[6] The problem was studied experimentally, and many of the findings have since become classic, such as the experiments on the part played by the ventricular muscle in the causation of the first sound. These studies were of the greatest value in that they clarified the whole problem, mainly by demonstrating the absurdities of most of the current theories of the day.

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The advent of the graphic methods of recording soon made possible a more precise analysis of the different phases of cardiac activity and afforded a method that allowed one to ascertain the exact moments of production and other peculiarities of the heart sounds.

The time relations between heart sounds and cardiac events was an additional contribution to the elucidation of the causes producing the heart sounds.

It is now certain that at least four sounds may occur, under normal conditions, during the heart cycle. Two of them, the classic first and second sounds, are heard on any living person. A third heart sound may be heard during early diastole in many young persons after the second sound, and the fourth sound, also called auricular, takes place and may often be heard immediately before the first sound during auricular systole.

THE FIRST HEART SOUND

The first heart sound is certainly a complex phenomenon, and although there is no general agreement concerning the conditions that produce it, there is no doubt that they are numerous. In fact such a multiplicity of causes explains most of the discrepancies existing between the findings of different investigators. Each investigator, using some special technic, has taken account only of the factors that his own particular method revealed, and has ignored the existence of all that it was unable to detect. Here, as elsewhere in science, the existence of such discrepancies is a clear demonstration of incomplete knowledge of the subject, and this is due largely to inadequacy of the procedures employed. With improvement in technic a more objective study can be made, discrepancies gradually disappear, and knowledge of the subject becomes solid and well founded.

There is experimental and clinical evidence that the following events produce vibrations contributing to the formation of the first sound: muscular contraction and tension of the ventricular walls at the onset of ventricular systole (muscular factor); closure of the auriculoventricular valves (valvular factor); movements and distention caused by the

ejection of blood from the ventricles into the arteries (vascular factor); and residual vibrations due to the preceding auricular contraction (auricular factor).

Before each one of these factors is analyzed it should be mentioned that sounds of the type observed in semioccluded arteries (Korotkow sounds), which may be produced by the action of the ventricular muscle on the coronary arteries, have also been suggested as an additional cause of the first heart sound (Laurell[7]).

It should also be emphasized that the factors mentioned above have not been listed in order of their relative importance. This will be considered below, for it varies according to the conditions and with the site of auscultation. However, almost everyone will agree that the valvular factor is the most important of all.

Muscular Component

The existence of a muscular component in the first heart sound was debated for a whole century and is still a matter of dispute.

In 1835–1840 the Committees appointed by the British Association for the Advancement of Science[6] showed that a muscular factor was responsible for a great part of the first heart sound, for this could still be heard after closure of the auriculoventricular valves had been prevented by the introduction of a finger into the auriculoventricular orifice. Ludwig and Dogiel,[8] in 1868, arrived at similar conclusions by placing ligatures in the auriculoventricular groove in dogs so as to prevent the free movement of the valves. They assumed that the sound still heard in such conditions was due to friction between muscle fibers at the beginning of systole. Yeo and Barrett,[9] in 1885, Krehl,[10] in 1889, Kasem-Beck,[11] in 1890, and Hess,[12] in 1920, repeated the experiments and confirmed the results of Ludwig and Dogiel.

A dissident view appeared in 1933, when Dock[13, 14] interpreted his experiments, which followed the Ludwig and Dogiel pattern, as indicating that the first heart sound disappeared when the valvular motion was prevented. Subsequent experiments, however, along the same line have led Smith[15] and Smith, Gilson and Kountz[16] to the conclusion that elements initiated by the heart wall contribute to the production of the first sound.

Eckstein[17] approached the problem from another point of view. To ascertain whether or not myocardial tissue from a mammal's heart produces a sound during contraction, he removed the heart from a cat immediately after death and perfused the coronary vessels from a cannula placed in the aorta. While the heart continued to beat, the right coronary and the left circumflex branches were ligated. All the ventricular musculature was then cut away except a V-shaped strip surrounding the left ramus descendens. The weight of this strip averaged about 6 gm. After ligation of the small vessels the strip continued to beat, and with the occasional help of epinephrine the beat could be made forceful. When a receiver was sewed to such a strip of ventricular muscle devoid of valves, chordae tendineae and ventricular chambers, vibrations were still heard and recorded during contraction. The vibrations increased in amplitude and number after epinephrine, and this showed that they depended upon the vigor of contraction. That skeletal muscle produces a sound when it contracts has been known since the classic demonstration of Wollaston[18] in 1810.

The muscular factor may not be essential for the production of the first heart sound, but until further evidence is available it would be incautious to deny that muscular contraction per se is able to originate sound vibrations.

Apart from the muscular sound discussed above, which is assumed to be due to the friction of the fibers against each other, it has been suggested that vibrations due to sudden tension of the ventricular walls also contribute to the formation of the first sound. This idea was put forward in 1895 by Geigel[19] and shared by Goldscheider,[20] Frank and Hess[21] and Hess.[22] It has been expressed with slight variations by Frey,[23] Schütz[24] and Weber.[25]

Current discussions of the causes of the heart sounds do not neglect the possibility of a muscular component in the first heart sound. In one of the latest reviews on the subject Rappaport and Sprague[26] state that "in spite of conflicting experimental evidence, it appears likely that contraction of the ventricle produces vibrations in the absence of valve closure. These (vibrations) contribute to the early part of the first sound."

On the clinical side, White,[27] in his well known textbook on diseases of the heart, says, "the first sound, loudest at the apex, is produced by closure of the mitral and tricuspid valves, plus an element of muscular contraction."

Valvular Component

Rouanet,[28] in 1832, seems to have been the first to regard the closure of the auriculoventricular valves as an important, or indeed the only, factor in the origin of the first heart sound. Obviously, of all the cardiac structures the valves seem the most likely to produce a sound by their closure. Said Rouanet: "They are thin, resistant, and inextensible, and pass suddenly from flaccidity to a state of very great tension," and this process explains the mechanism of production of the sound.

Bayer,[29] in 1869, and Giese,[30] in 1871, showed that if, in a dead heart with artificial circulation, the auriculoventricular valves were suddenly placed in tension, a sound was produced.

The changes in the characteristics of the heart sounds following valvular defects created by disease are further proof of the paramount importance

of the valvular factor for the production of the heart sounds.

No matter how obvious it seems to consider the vibrations of the valves as a main cause of the heart sounds, dissident views have also appeared. Just as an example of how positive a man can be in affirming or denying the role of the heart valves in the production of the heart sounds, Kassatkine,[31] a Russian investigator, considered himself justified in concluding that "the tendency to consider the heart sounds as a valvular sound is a mistake." He believes that the view of those who attribute the origin of the sounds to the vibrations of the heart walls and of the walls of the aorta and pulmonary arteries adjacent to the valvular orifices is more convincing.

Vascular Component

Even in the earliest writings on the subject, the idea was expressed that vibrations due to the opening of the semilunar valves took part in the formation of the first sound (Cruveilhier,[32] in 1841, and Ceradini,[33] in 1872).

Bamberger,[34] by simple auscultation, had concluded that during systole, when the first sound is heard, four sounds, which are superimposed and usually heard as two, are produced — namely, the tricuspid and mitral sounds, and those caused by distention of the pulmonary artery and aorta.

The pioneer records of the heart sounds taken by Einthoven and Geluk[35] showed a delay of about 0.06 second for the first sound recorded at the base of the heart, as compared with the same sound recorded at the apex; they therefore thought that the first sound at the base was due to the opening of the semilunar valves.

The part played by a vascular component in the genesis of the first heart sound was denied on the basis that this sound did not spread to any extent during the ejection phase of ventricular systole. This can no longer be doubted after phonocardiographic observations in animals (Wiggers and Dean[36]) and in man (Schütz,[37] Weber[25] and Caeiro and Orías).[38]

My own experience has shown that in human phonocardiograms obtained from the chest, it is extremely common to find that the first sound is composed of two principal groups of vibrations (Orías and Braun-Menéndez,[39] Orías[40] and Caeiro and Orías[38]). The records demonstrate clearly that one of these corresponds to the systolic isometric phase and the other to the ejection phase of ventricular systole. If the heart sounds are explored from different sites it is always possible to show this division appearing in at least one such area of auscultation either constantly or else during certain moments in the respiratory cycle (Caeiro and Orías[38]).

In fact, from the careful study of a large number of phonocardiographic tracings we are convinced that vibrations of vascular origin form an important and as yet not sufficiently recognized proportion of the first sound as heard over the precordial area in normal conditions.

When, by reason of favorable circumstances the separation of the components of the first heart sound occurring during the isometric and the ejection phases of the ventricular systole is more accentuated, a true splitting of the sound may be recognized by auscultation and recorded by the phonocardiograph.

Auricular Component

The idea that vibrations of auricular origin contribute to the formation of the first heart sound has suffered many vicissitudes. The earliest records made of the first sound showed that this began 0.02 to 0.04 second before ventricular systole, which led some workers like Hürthle,[41] Pawinsky,[42] Weiss[43] and Roos[44] to believe that the initial vibrations were of auricular origin.

Later records showed that, although the earliest vibrations of the first sound sometimes preceded ventricular systole, they appeared *after* auricular systole (Battaerd[45] and Wiggers and Dean[36]). This observation, together with the fact that when a separate clearly auricular sound existed, as in cases of gallop rhythm, these auricular vibrations preceded those of the first sound by a longer interval, led Wiggers[46] to deny the possibility of auricular participation in the formation of the normal first sound. In his opinion the small and slow initial vibrations that precede ventricular systole had not received an adequate explanation.

When more sensitive recording devices were used, especially in cases of delayed auriculoventricular conduction (incomplete, partial and complete auriculoventricular block) and in cases of transitory nodal rhythm, it was shown that late manifestations of auricular activity contribute to the formation of the first heart sound.

Braun-Menéndez and Solari,[47] by recording the heart sounds direct from the ventricular wall in dogs with auriculoventricular block, found that auricular contraction can produce sound vibrations persisting 0.20 second after the beginning of auricular systole and forming two groups of vibrations in the sound record. The first group of vibrations coincides with auricular contraction, but the second group appears during full auricular diastole.

These facts satisfactorily meet Wiggers's objection that the auricular sound, when present, does not merge into the first sound. What happens is that when the first component of the auricular vibrations is sufficiently strong to be recorded, a clear auricular sound is observed, well separated from the first heart sound. In ordinary conditions it is the delayed components (second group) that contribute to, and so reinforce, the first sound.

The Second Heart Sound

The origin of the second sound is much simpler than that of the first, and was well understood even by the very earliest investigators of the heart sounds.

The connection of the second heart sound with the closure of the semilunar valves was first precisely proposed and demonstrated by Rouanet[28] in 1932. He found that sudden stretching of an elastic membrane is always accompanied by a more or less distinct "snap," and on the basis of this simple experiment he could demonstrate what happens when the second sound is produced.

He inserted a vertical tube into the upper portion of an excised aorta, and into the other end, below the valves, another tube connected to a rubber balloon filled with water, which was compressed rhythmically. Each time that by decompression of the rubber balloon the reflux of the column of liquid was stopped by the semilunar valves, a sound could be heard if the ear was applied to the tube. Rouanet's explanation was adopted by Billing,[48] Carlisle[49] and Bouillaud.[50] His experiments were repeated and confirmed by the British Committee.

All the later anatomic, clinical and experimental observations have adduced new proofs in favor of the idea that the closure of the semilunar valves is the essential cause of the second sound, which is the acoustic expression of vibrations set up at this moment in the valves, in the walls of the artery and also in the blood column itself (Webster[51]).

In the ordinary conditions in which auscultation is made, the sounds originating in the aorta and the pulmonary artery, respectively, are heard as only one sound owing to summation. In cases of asynchronous closure of the semilunar valves, a reduplicated or split second sound is the result. The asynchronous closure of the semilunar valves as a cause of the split second sound was expressed without any objective basis before the phonocardiographic era but is now supported by experimental facts (Katz[52] and Braun-Menéndez and Solari[53]).

The Third Heart Sound

Many hypotheses have been proposed to explain the origin of the third sound. Here also, to a greater or lesser extent either the valves or the heart walls, or both, have been held responsible for the vibrations originating the sound.

Einthoven[54] thought that the third sound was caused by vibrations set up by sudden tension of the semilunar valves, but without definite statement of why this phenomenon should occur.

Gibson[55] and Hirschfelder[56] attributed the third sound to a transient and sudden closure of the auriculoventricular valves after the rapid filling of the ventricles. Gallavardin,[57] Benjamins[58] and Bridgman[59] supported this view. The study of venous pulse tracings optically recorded simultaneously with phonocardiograms eliminates, however, the possibility of any such valvular movement occurring at the moment at which the third sound is produced (Braun-Menéndez and Orías[60]). Nor could Dean,[61] by experiments in dogs, verify the existence of a valvular apposition at the time when the third sound is produced.

The third sound is produced in the final moments of the rapid ventricular filling as shown by its very constant relation with the last portion of the descending limb of the V wave (Ohm[62] and Braun-Menéndez and Orías[60]). From this observation the hypothesis has been advanced that the third heart sound is caused by vibrations of the ventricular walls that are due to their sudden distention by the inrush of blood from the auricles in the final moments of rapid ventricular filling. This conception was proposed by Ohm[63] and has been supported by Frey,[23] Lian,[64] Gubergritz,[65] Melik-Gülnasarian,[66] Leonhardt,[67] Schütz[24] and Braun-Menéndez and Orías.[60]

By the term "ventricular walls" no distinction is implied between muscular and tendinous structures or valves. Furthermore, although the cause given above is stressed as the principal one, subsidiary factors should not necessarily be excluded.

The intensification of the third heart sound under special pathologic conditions implying myocardial damage as happens in some cases of gallop rhythm is further evidence of a muscular component in the genesis of the third sound.

Boyer[68] has presented experimental evidence to show that vibration of the ventricular wall produced in the quiescent heart by a very feeble impact gives rise to a sound very like the normal third sound in frequency, amplitude and duration.

On the clinical side, White[27] states: "The third sound is probably the result of the vibration of the ventricular walls and auriculo-ventricular cusps caused by the inrush of blood every diastole."

Causes of the Auricular Sound

One of the most important contributions made by the graphic method to the study of the acoustic manifestations of the heart's activity has been the recognition that, even in normal conditions, auricular contraction produces vibrations having the properties of sounds that are undoubtedly often heard at the surface of the chest in healthy persons, even under the ordinary conditions of auscultation.

During auricular activity various phenomena may produce a sound. Acoustic vibrations may be produced during auricular contraction by the muscular contraction itself as pointed out by Krehl,[10] Roos,[44] Weber and Wirth,[69] Benjamins,[58] Reid,[70] Mond and Oppenheimer[71] and Fogelson[72]; the tension of the auricular walls; the passage of blood through the valvular orifices (Kahn[73]); the distention of ventricular walls by the inrush of blood from

the auricles (Bridgman[74]); and the friction of the auricle against neighboring structures.

Once auricular contraction itself is finished, there is a possibility of residual vibrations in the above structures, and of new vibrations (Melik-Gülnasarian[75]) owing to the movement of apposition of the auriculoventricular valves at the end of auricular contraction.

All these factors probably combine in different proportions to produce the auricular sound, and account for its complexity in phonocardiographic records when it occurs separate from the first sound as in cases of auriculoventricular block (Braun-Menéndez and Solari[47]).

The intensification of the auricular sound under special pathologic conditions implying myocardial damage, as in some cases of gallop rhythm, is further evidence of a muscular component in the genesis of the auricular sound.

Summary

There is experimental and clinical evidence pointing to four factors as contributing to the formation of the first heart sound: muscular contraction and tension of the ventricular walls at the onset of ventricular systole (muscular factor); closure of the auriculoventricular valves (valvular factor); movements and distention caused by the ejection of blood from the ventricles into the arteries (vascular factor); and residual vibrations due to the preceding auricular contraction.

The second heart sound is due to vibrations produced by the closure of the semilunar valves on the valves themselves, in the walls of the arteries (pulmonary and aorta) and also in the blood column.

The third heart sound is caused by vibrations of the ventricular walls due to their sudden distention by the inrush of blood from the auricles in the final moments of rapid ventricular filling.

Muscular contraction and distention, passage of blood through the auriculoventricular orifices, distention of ventricular walls by the inrush of blood from the auricles and friction of the auricle against neighboring structures are the underlying factors accounting for the auricular sound.

Discussion

Dr. William Dock*: Dr. Orías has given an excellent historical and critical review of the heart-sound problem, to which I have nothing to add. However, I should like to do some subtraction and to recapitulate my heresies, already incorporated in two papers and presented to the sophomores each year until Dr. DiPalma decided that it was not advisable to continue confusing the class in physical diagnosis.

Of the animal experiments, the crucial one is that of Macleod and Cohn,[76] who inserted a piezoelectric device into dogs' hearts, through the carotid artery or the jugular vein, to record the pressure synchronously with the electrocardiogram. Such a system records sound vibrations if they are intense, and the records show clearly that the first sound is intense only at the auriculoventricular orifice, although vibrations are recorded, synchronous with the first sound and with ejection, at the aortic orifice. The second sound is intense only at the aortic orifice. These observations seem to me to show that the dog's aorta, unlike its brachial and femoral arteries, does not give off a pistol-shot sound when the pulse wave enters it; they show that the first sound originates in the auriculoventricular, and the second in the semilunar valves. No vibrations of audible frequency were recorded from either the auricular or the ventricular walls with which the pick-up came in contact; the vibrations became attenuated rapidly a few centimeters away from their points of origin. In a continuous medium — air, water or steel — sound is attenuated according to the usual square of the distance formula; in discontinuous mediums — cork, rubber, air full of rain or snow, plasma full of red cells or muscle — sound is attenuated very quickly. Fibrous structures or crystalline structures, such as bone and tendon, transmit sound fairly well. The aorta and pulmonary-artery walls are better sound conductors than the ventricles, and the aortic and pulmonic sounds are loudest at the points where the vessels come closest to the thoracic wall, not where the stethoscope is closest to the valves. The auriculoventricular valves insert into the annulus close to the great arteries, and the first sound is transmitted to and along these vessels. First sounds, greatly attenuated, also pass out to the chest wall through the ventricular muscle mass. With a stethoscope, one can hear the heart sounds of a mouse or a horse; when the heart is exposed and in the hand, even if the ear is placed fairly close, no heart sounds in dogs', calves' or horses' hearts are detected. If the muscle itself vibrated, the sound should be intense at the surface. A violin string plucked so as to set up vibrations as intense as those recorded at the auriculoventricular valve by Macleod and Cohn[76] when in contact with the recorder could be heard many meters away in air. It is not remarkable that the heart sounds — damped by blood and meat, lung and adipose tissue — were unheard so long, even after Harvey.

I agree with Dr. Orías that the auricle, when it begins to contract, causes audible vibrations loudest next the esophagus, as shown by Taquini.[77] I think this sound is due to the sudden tensing of the valves of Vieussens and Thebesius, guarding the coronary venous orifices, which are just next to esophagus. This sound is never heard and rarely recorded from the surface of the body.

I agree that there is a pair of little clicks at the end of auricular systole, even when this occurs in mid-systole of the ventricles with the auriculoventricular valves firmly closed. This is believed to be due to the snapping back and forth of the interauricular septum as systole dies out first in one auricle and then in the other and venous blood surges in. During all the rest of auricular systole, there is dead silence — muscular contraction and interfibrillar friction occur, but what sound is produced is quenched before reaching the cavity or the surface of the auricle.

During ventricular systole there is dead silence except for a brief snap as intraventricular pressure begins to rise. Here, also, all sound due to motion and friction is quenched at its source. If the heart is empty, or if it contracts early in diastole before isometric relaxation has ended and ventricular filling begins, there is dead silence, as one may observe in early ectopic beats. Here a contraction only a few thousandths of a second later in diastole, when the heart is filling but so empty that the weak beat fails to open the semilunar valves, causes a very loud first sound. In heart block, auricular fibrillation and ventricular tachycardia one regularly observes that beats occurring late in relation to phases of ventricular filling cause weak first sounds; those near the peak of a wave of filling cause loud sounds even when, as in ventricular tachycardia, the patient is pulseless and the second sound absent in the same beat.

Caudal to the third rib the first sound is almost purely valvular, but at the base vascular elements enter into it and the peak intensity may occur 0.02 to 0.04 second later than at the apex. First sounds at the base vary in intensity less than at the apex, in the conditions named above. Rarely, the ear can detect splitting at the base in first sounds not split at the apex, so that the vascular element is distinct from the valvular element. Both elements arise in fibrous structures suddenly made taut by rising pressure, but even in anemia and aortic insufficiency the first sound at the base, in spite of the vigorous pulse wave and the closeness of the great vessels to the chest wall, is less intense than the apical first sound. Even at the base, the vascular vibrations may

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be less intense and record only as small late oscillations, with the peak of intensity synchronous at base and apex.

Dr. Orías has properly stressed the contribution made by the vascular vibrations in determining the character of the first sound at the base. Most split first sounds, even at the base, are due to a synchrony of events on the two sides of the septum, not to separation of valvular and vascular elements. I am not aware of any clinical significance attached to detectable variations in the first sound as heard at the base, but such correlations may be noted in future by those who study these two factors at the bedside or in records of the sounds.

The auricular element recorded as blending into the first sound seems related to presystolic gallop. It might be called a belated, weak presystolic gallop, or fourth sound. These sounds, whether protodiastolic and due to early passive filling or late and caused by auricular systolic ejection, are not the result of tension in the ventricular walls. Apical records and border motion records made with the x-ray apparatus show that further filling follows the protodiastolic gallop or third sound, so that the ventricle could not be taut like a blown-up paper bag. Actually, the diastolic ventricle is never taut in that sense. If one prevents outflow in a dog's heart by clamping the aorta or inducing ventricular fibrillation, it balloons up to twice the volume normally reached in diastole; if the pericardium is then cut away it nearly doubles in volume again. In diastole the muscle is a jelly, capable of being drawn out to twice or thrice its usual diastolic column. If a Valsalva experiment is performed on a normal person with third sounds the heart shadow is far larger than during normal diastoles in which third sounds were recorded. The third and fourth sounds and the gallops occur when pressure between auricle and ventricle become equalized; the apex and lateral wall move basalward at this time; blood moves toward the auricle, and the valves may be drawn taut so quickly as to cause a sound louder than the first sound. If the patient has mitral-valve disease, and has a systolic murmur, the gallop, like the first sound, may be followed by a murmur, as Rytand has clearly demonstrated. Therefore, it is concluded that all sounds heard between the second sound and the true, or auriculoventricular, first sound are due to tension of the valves at the end of a wave or rapid inflow.

To summarize, the apical first sound and all the third and fourth sounds and gallops are due to tension of the auriculoventricular, and the second sound to tension of the semilunar valves. The basal first sound may contain elements, or rarely a distinct split sound, owing to the shock in the wall of the great arteries; usually, in man the pulse wave causes no sound in the aorta, and in dogs, in which brachial and femoral vessels have normally a pulse sound, the aorta has none, or a very feeble one. Most split first sounds are due to ventricular asynchrony.

The ventricular muscle is a good sound damper, as in the blood itself. The great vessels transmit sound fairly well.

The views expressed by Levine and Harvey[78] differ from those of White,[27] just as mine do from those of Dr. Orías. Whether cardiologists live in the same town or in different hemispheres, clinical experience and honest careful study of their own and their colleagues' observations may lead them to diametrically opposed or deviant views. If this leads to further study, the profession has a future; when it leads one to believe his own or someone else's dogma, and stops experiment, the profession is dead.

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THE PHYSIOLOGIC COMPONENTS OF THE URINARY BLADDER*

Their Clinical Significance

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THE study of bladder function by cystometry has led to the conclusion that the bladder acts as a single unit. This was inevitable, since the cystometer registers the summation of changes in intravesical pressure resulting from detrusor contraction, without disclosing how such changes are brought about. Observation of the bladder during micturition under the fluoroscope, however, makes it quite clear that this concept is not entirely correct.

There are two functional units of the bladder that, by their synergism under normal circumstances, comprise the total detrusor function. These two units, which consist of the bladder base and of the dome, have a separate embryologic origin. The dome of the bladder develops from the cloaca, and is thus entodermal in origin, and the base is formed from the wolffian ducts and therefore stems from mesodermal tissue.[1] The base of the bladder is thicker than the dome, and this fact is of physiologic significance.[2] The function of the dome and of the base of the bladder can become separated under certain pathologic conditions, with the result that the dome will seriously hamper the action of the bladder base, and micturition then becomes inefficient. This pathologic state is more easily understood if the sequence of events in normal micturition in man is kept in mind.

In a previous paper[3] it was pointed out that man has a distinct voluntary mechanism with which he starts and stops micturition. This mechanism uses the pubococcygeus, a large, paired, striated muscle with a somatic nerve supply, which, when relaxed at will, causes the region of the internal sphincter to drop downward. It is the displacement of the internal sphincter that precipitates the reflexes of micturition. The reflex for the ensuing detrusor contraction starts at the vesical neck and then propagates symmetrically and bilaterally to the base, to the sides and lastly to the dome of the bladder, so that at the beginning of micturition, after the downward tug on the internal sphincter, one can see quite clearly the contraction of the base followed by the rather marked contraction of the sides of the bladder. The bladder dome is thus raised, and at this moment the vertical diameter of the bladder becomes considerably greater, whereas the transverse diameter becomes smaller. At the moment micturition is deliberately stopped, the vesical neck becomes sharply elevated by the contraction of the levator ani muscles (including the pubococcygeus), the internal sphincter is shut, and first the base, then the sides and gradually the dome can be seen to relax, so that the vertical diameter of the bladder becomes smaller, and the transverse diameter larger (Fig. 1). It will thus be clear that the bladder neck is the site at which the stimulus for the contraction of the detrusor originates, and from which the signal

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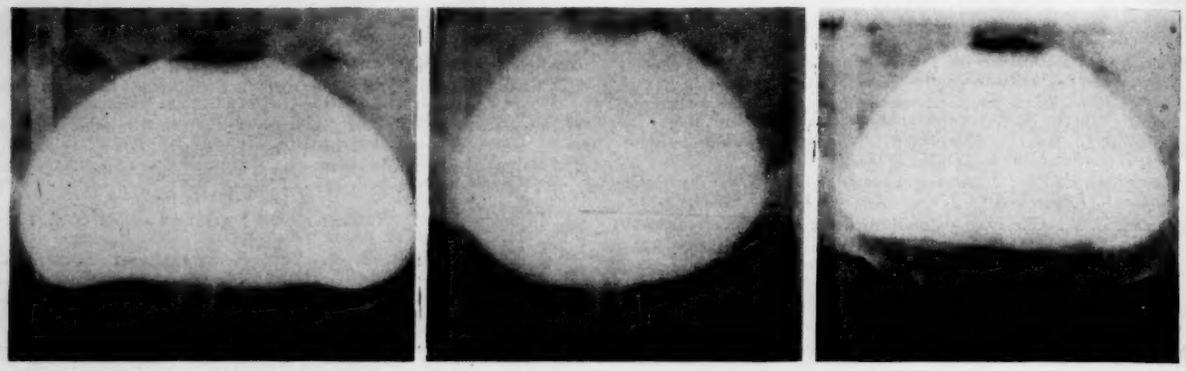
for its relaxation spreads. The bladder base with its thicker musculature is therefore the primary expulsive motor force, and the dome facilitates the uninterrupted emptying of the bladder by contracting progressively and thus serving an important auxiliary function. It is the contraction of the dome that directs downward toward the internal sphincter the increased hydrostatic pressure, resulting from the contraction of the base. The foregoing remarks are based on about 200 careful fluoroscopic observations of the function of the bladder in normal and in pathologic conditions. The study of bladder behavior in obstructive and in various neurologic dysfunctions was helpful in an interpretation of the events in the normal person.



A B C

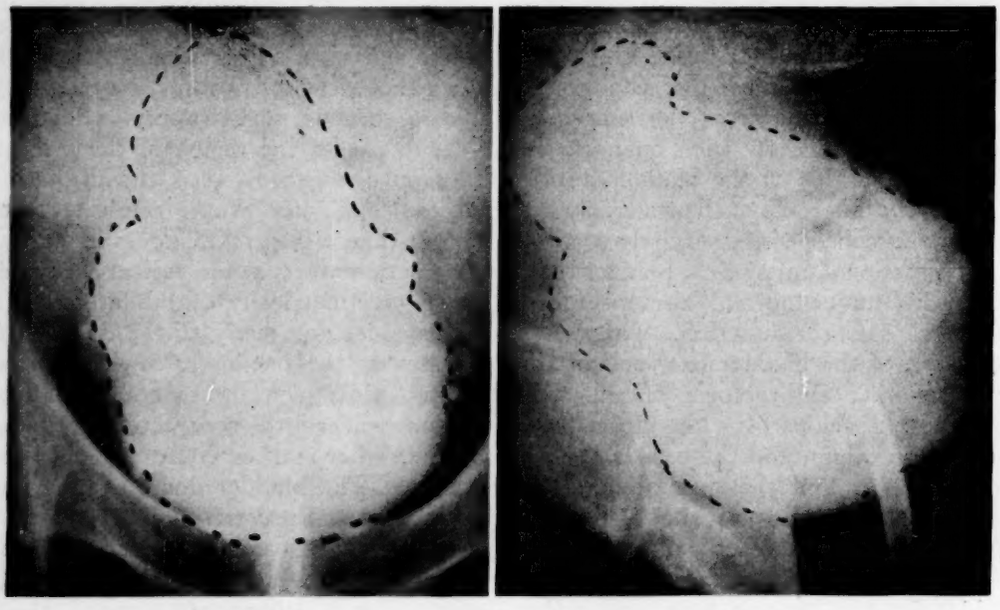
FIGURE 1. *Urinary Bladder in a Normal Male.*

A = *bladder at rest (note the shape of the bladder base, and its relation to the symphysis pubis).*

B = *bladder during micturition (note the shape and the descent of the bladder base; the vertical diameter is now larger, and its horizontal diameter is smaller compared to its shape during the resting stage).*

C = *bladder immediately after deliberate cessation of micturition. (The base and the dome have resumed the contour shown in A.)*

The thinner structure of the dome and its greater motility make it particularly suited to take up unusual pressure and volume changes of the bladder in certain obstructive or neurogenic vesical disturbances. Under such circumstances the dome and also the sides of the bladder can become markedly overdistended to accommodate the considerably



A B

FIGURE 2. *Urinary Bladder in a Case of Cancer of the Prostate.*

A = *anteroposterior view.*

B = *oblique view (note dilatation of the dome).*

larger quantity of urine (Fig. 2). A bladder that has thus become quite large and overstretched loses much of its contractile power, and if micturition is possible at all, it will be accompanied by large residua. This loss of efficiency, however, may be only temporary, and the detrusor can recover much or all of its contractile power after the removal of an obstruction or after rehabilitation by means of drainage or other appropriate therapeutic measures in neurogenic vesical dysfunctions.

The shape of the bladder dome in obstructive conditions will vary, depending on the degree and the rate of development of the obstruction. The dome can hypertrophy evenly with the rest of the bladder, and the bladder configuration on the cystogram, except for the thickened bladder wall, may then resemble that of the normal organ. On the other hand, the bladder base may hypertrophy to twice the thickness of that of the dome so that with increasing failure of the detrusor to empty, the thin dome may balloon out considerably and assume a cystographic silhouette, as shown in Figure 3. In

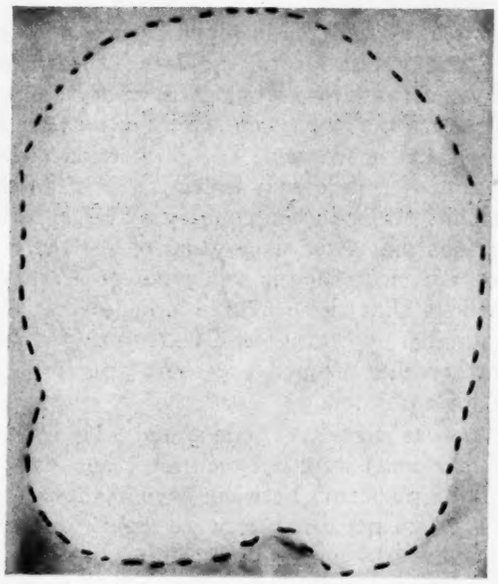


FIGURE 3. *Urinary Bladder in a Case of Benign Prostatic Hypertrophy.*
Note the enormous dilatation of the dome.

neurogenic vesical disturbances that lead to a big and overdistended bladder with large residua, the dome may become distended to enormous proportions (Fig. 4). When the dome has become markedly overdistended by whatever cause, it fails to assist the bladder base in the expulsion of urine. When the patient is still able to elicit a contraction wave from the bladder neck to the base upward, this wave tends to dissipate toward the dome, and the resulting slight increase in intravesical pressure may balloon out the dome somewhat further. It is under such circumstances that the patient literally "voids into the dome of his bladder." In neurogenic vesical dysfunctions when the contraction of the detrusor has become enfeebled by overstretching, a large, dilated and therefore quite useless bladder dome may nullify the efforts of the detrusor to void. An overdistended noncontractile bladder dome therefore fails the detrusor in two respects. Being overdistended and noncontractile, it does not propagate or enhance the peristaltic wave, and by the same

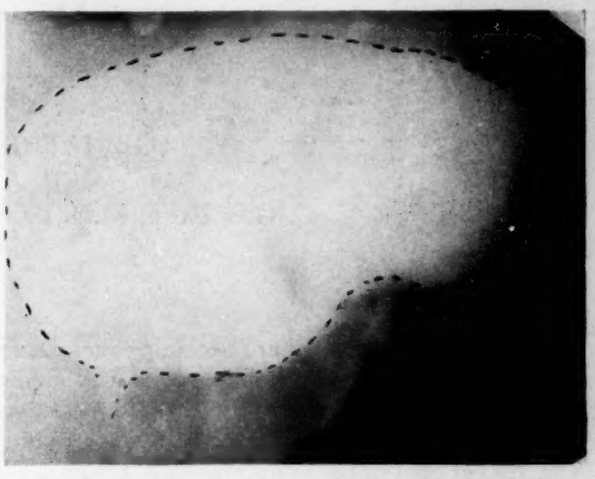


FIGURE 4. *Urinary Bladder in a Tabetic Patient (Oblique View).*
Arrows point to the markedly dilated bladder dome.

token, it wastes the increase in hydrostatic pressure that results from the contraction of the base and of the sides of the bladder, by directing much of that force upward toward the dome instead of downward toward the bladder neck.

To improve the efficiency of micturition under such circumstances it is necessary to correct these anatomic and physiologic changes of the bladder. In most cases this can be readily accomplished. If these changes, however, prove to be permanent, mere concentration on the vesical neck, or on means to stimulate the detrusor, will not restore adequate micturition. Under such circumstances improvement can be achieved if the useless bladder dome is excised. The resultant small bladder, which consists essentially of the bladder base and of its sides, can become a surprisingly efficient expulsive organ. In a previous communication,[4] the beneficial results of such an operation in certain cases of prostatism was pointed out. Moreover, this procedure ought to be of value whenever the bladder dome irrevocably becomes a useless pouch. Resection of the bladder dome, however, is reserved only for patients in whom its permanent uselessness is demonstrated, and it ought not to be undertaken if its contractility can be restored by conservative means. The indication for this operation, therefore, must be carefully

established on an individual basis, and in conjunction with other measures calculated to remove obstruction and to enhance detrusor tonicity.

Summary

The urinary bladder in man is made up of two integrated functional units, which consist of the bladder base and dome. These two units have a separate embryologic basis and differ in their physiologic function. The bladder base is the primary motor force in micturition, and the bladder dome acts in an auxiliary manner. Under certain pathologic conditions, the bladder dome can become permanently overdistended and noncontractile. When this occurs, the dome interferes with the expulsive efforts of the base, and micturition becomes inefficient. Excision of the useless dome remarkably increases detrusor efficiency.

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GERIATRIC DERMATOSES*

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DISEASES of the aged are becoming increasingly important in the economic, social and medical life of the country. Whereas in 1910 only 4.3 per cent of the population were sixty-five or over, in 1950, 7.9 per cent of the population will be in this age group, and in another ten years, 10 per cent of the population will have reached this age. Thus, the diseases of this group require and will continue to require greater attention on the part of all physicians. In addition, the infirmities accompanying the aging process are apt to be slower in responding to treatment or to become more chronic so that more individual medical attention is required.

From the medical standpoint the diseases of this age group affect many systems of the body, and it is seldom that only one system is involved. The skin and its accessories participate in the changes of advancing years, but little attention has been paid to the part that these cutaneous disturbances may play in the life of the person affected. Many of these manifestations on the skin persist because of some other disease or condition, such as a circulatory abnormality, nutritional deficiencies, lack of proper care, failure to realize implications of a relatively insidious onset and often a real neglect. Thus, the disturbances on the skin must be considered in the light not only of the age of the patient and his general medical condition but also of various other factors.

Since comparatively little attention has been given specifically to the skin disturbances of this age group it seemed of interest to review the records of 2000 private patients over sixty years of age for the purpose of determining the diagnosis of their diseases and discussing them.

This survey was made several years ago and included many records of the late Dr. Arthur M. Greenwood, as well as our own records. Of these 2000 cases, 785 (40 per cent) were in men, and 1215 (60 per cent) in women. The proportion of women to men in these figures is much higher than that in Massachusetts or in the country at large, although it is a fact that after sixty years of age the proportion of women to men is somewhat greater. We do not believe that these figures indicate that women have a higher percentage of disease in this age group, but rather that women are more apt to seek the advice of a physician.

So far as ages are concerned, 1145 patients (57.25 per cent) were between sixty and sixty-nine, 677 (33.85 per cent) between seventy and seventy-nine, 170 (8.5 per cent) between eighty and eighty-nine, and 8 (0.4 per cent) over ninety years of age. A characteristic distribution according to age and sex among 1000 patients is shown in Table 1.

Table 2 presents data concerning the most common skin diseases found in this group.

Although these figures do not indicate the frequency with which the diagnoses would be observed in patients given a general examination in this age group, it will be seen that senile keratosis (the precursor of epithelioma), epithelioma, seborrheic keratosis, eczema and contact dermatitis were the most common conditions for which older patients consulted a dermatologist, or at least the most common conditions found on examination by a dermatologist. One wonders if the relatively large number of cases in the first three groups was due mainly to campaigns against cancer carried out over a period of years. Certainly, far fewer neglected cases of

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skin cancer are seen, and many more persons consult physicians for relatively insignificant growths on the skin in comparison with conditions twenty or twenty-five years ago.

Thus, the five most common diagnoses include 1057 cases, or 50 per cent, the next ten diseases 1439, or 72 per cent, and fifteen diseases 1558, or 78 per cent. Many of these conditions are common to many ages and not necessarily restricted to this particular age group (see Table 2).

Not included in this group are conditions commonly occurring in older persons — that is, conditions that would be found on a general examination in a large group, such as dry skin, atrophy, pigmented areas, graying of hair, thinning of hair, brittle nails and small tumors of various types. Many questions are asked on these subjects by patients being examined for other cutaneous disturbances.

In addition to this group, there was a group of relatively common dermatoses, which occurred less frequently among elderly patients. Table 3 demonstrates the diseases observed next in frequency. These are not particularly caused by increasing age but appear in the general population.

In Table 4 are listed relatively unusual dermatoses observed in this group. These usually occur at a somewhat younger age, but they have been noted in this series of older persons. Rare or unusual diseases were present in less than 5 per cent of this series.

More commonly observed in younger persons — that is, in those under sixty — are such diseases as rosacea, impetigo, pityriasis rosea, scabies, intertrigo, erythema induratum, molluscum contagiosum and pediculosis. As a matter of fact, they can occur at any age, but they are much more frequent below sixty. Rosacea was seen more often in women than in men (this condition is usually more apparent among patients thirty to fifty years of age). Erythema induratum, of course, is more frequent on the legs of female patients between ten and thirty, although 2 cases were seen in this group. Impetigo occurring in the older age group is often more obstinate than that seen in children. In certain cases it has responded very slowly, but such cases have been more responsive to penicillin than to some of the older antiseptic drugs previously used. Other diseases in this group were not seen very frequently.

It has been a surprise to us that there have not been more cases of certain diseases in these 2000 cases. There were only 2 cases of varicose ulcer and 13 cases of an eruption due to drugs, though it is possible that some of the cases of toxic erythema were drug eruptions. Leukoplakia would be thought to occur more often in this age group, and kraurosis vulvae, of which only 1 case was observed, is described much more frequently at this age. It is also surprising that more persons do not present themselves for graying or loss of hair. These items are expected perhaps as a part of growing old, although the advertisements of newspapers and magazines

TABLE 1. *Age Group in Relation to Sex in 1000 Cases.*

Age Group	Men	Women	Totals
yr.			
60–69	239	305	544
70–79	163	197	360
80–89	33	60	93
Over 90	1	2	3
Totals	436	564	1,000

TABLE 2. *Most Common Skin Diseases.*

Disease	Men	Women	Totals
Senile keratosis	119 (5.9%)	169 (8.4%)	288 (14.4%)
Epithelioma	126 (6.3%)	160 (8.0%)	286 (14.3%)
Seborrheic keratosis	71 (3.5%)	105 (5.2%)	176 (8.8%)
Eczema	104 (5.2%)	72 (3.6%)	176 (8.8%)
Dermatitis, contact	65 (3.2%)	66 (3.3%)	131 (6.5%)
Pruritus	44	54	98
Psoriasis	38	55	93
Seborrheic eczema	28	51	79
Dermatophytosis	39	26	65
Verrucae	12	35	47
Acne rosacea	7	30	37
Urticaria	6	16	22
Lichen planus	9	12	21
Herpes zoster	8	12	20
Syphilis	8	11	19

TABLE 3. *Common Dermatoses Less Frequently Noted.*

Condition	No. of Cases
Alopecia	17
Impetigo	16
Neurodermite	16
Hypertrichosis	15
Mole	15
Dermatitis medicamentosa	13
Bacterial dermatitis	12
Monilial infections	12
Toxic erythema	12
Leukoplakia	12
Ulcer	11
Pityriasis rosea	10
Seborrhea capitis	10
Angioma	10

TABLE 4. *Incidence of Relatively Rare Diseases.*

Disease	No. of Cases
Pemphigus	11
Sarcoid	11
Multiple benign cystic epithelioma	9
Miliary lupoid	8
Melanotic sarcoma	7
Lymphoblastoma	6
Painful nodule of ear	6
Kaposi sarcoma	4
Lichen sclerosis et atrophica	5
Pseudopelade	3
Erythroplasia of Queyrat	3

may lure them when the dermatologists' pessimistic prognoses fail.

Before the more common dermatoses noted in this group are discussed it is hardly necessary to emphasize that senile cutaneous changes do not develop at any particular age. The onset of such changes is just as variable as the beginning of senile changes in the ear, eye, joints and arteries, and the rate of alteration varies greatly in different persons. In the general examination of older patients the physician finds that as the years pass the subcutaneous fat is lessened, the skin becomes less elastic and thinner, more wrinkling develops, the color may become grayish or yellowish, perhaps with pigmented or depigmented areas, and there may be a variable amount of dryness and scaling, especially in cold weather. There is also the appearance of gray and white hair, as well as the thinning and possibly entire lack of hair on the vertex in men. In addition, the physician will find in many older people hyperpigmented areas, especially on exposed surfaces, with varying degrees of pigmentation, including depigmentation, small capillary tumors or angiomas, small pedunculated fibromas, small verrucae, keratoses and so forth, many of which have been present so long or have developed so gradually that they are accepted by the patient as a part of the aging process.

Epithelioma

In this series it will be noted that skin cancer, or epithelioma, and its precursor, keratosis senilis, constitute the largest group of cases observed in this series: 574, or 28.7 per cent of the total number of cases. In fact, in many cases epithelioma and keratoses of both types were found in the same person. The number of women with epithelioma was very much larger than the number of men. In one of our groups the number of women with epitheliomas was almost twice that of the men. In that same series the proportion of brunettes was very much larger than blondes. The nose and cheeks accounted for more than half the cases. Cancer of the skin was found in two clinical types. The milder type — the basal-cell epithelioma — was usually a pearly nodule or ulcer with a pearly border and central crust, though there was considerable variation in its appearance. The more serious type — the squamous-cell epithelioma, which was less frequent — developed more rapidly, had more ulceration, was a deeper process and tended to metastasize.

When seen early these lesions were treated very satisfactorily with x-rays or radium; occasionally, desiccation was used, or excision advised. The dose of radium or x-rays was varied with the size and depth of the individual lesion, but an adequate border about the lesion was included and the dosage was sufficient to produce necrosis of the area. Excision must be wide enough to remove any possible extension of the tumor mass, and desiccation in the same way should include enough area to eradicate any fingerlike processes from the main tumor.

Cancer is a serious disease, but cancer limited to the skin does not have the relatively serious prognosis of cancer of the other organs. This abnormal process on the skin is external and visible or palpable, or both, and if treated properly and early in its development can be absolutely eradicated. In fact, it can be stated that mortality from skin cancer can be absolutely prevented by the co-operation of the patient in presenting himself for diagnosis at the earliest possible moment and by the co-operation of the physician in early diagnosis and complete eradication. However, if one considers in this group cancer on the lip and tongue and oral cavity, the seriousness of prognosis is greatly increased, and early diagnosis is of far greater importance.

The campaign against cancer has been most helpful as far as skin cancer is concerned, but perhaps more emphasis should be placed on this form of cancer. Much disfigurement and perhaps even death might be prevented by any form of lay campaign by medical or public-health groups emphasizing the desirability of reporting for examination of even minor, localized changes in the skin as the patient becomes older. In any such campaign at the same time physicians need to be reminded of possible malignant changes developing in apparently insignificant lesions in persons over sixty years of age. Of course, basal-cell carcinoma has been seen in the teens and twenties, but in the older age group it is much more frequent. The tumor clinics established in many hospitals, with a surgeon, radiologist and dermatologist in attendance, have been important factors in many communities in education about cancer in this age group, as well as furnishing diagnostic and therapeutic centers.

Senile Keratosis

As with epithelioma, the figures in this series indicate that these keratoses appear more frequently in women than in men. Senile keratoses are real precancerous lesions. They occur chiefly on exposed surfaces, and they are seen more commonly in persons much exposed to the sun and wind and in those of blond or "sandy" complexion. They may occur anywhere on the face, more frequently (in this series) on the forehead, upper cheeks, nose, ears, sides of the neck and dorsal surfaces of the hand. They are usually red, slightly scaly and quite sharply outlined, often with slightly or even tightly adherent crusts, which are sometimes dark, dry and often hard. These crusts frequently come off but soon re-form.

These lesions were destroyed by desiccation, radium or x-rays, or by trichloracetic acid adequately applied. A mild salicylic and sulfur ointment, 2 to 4 per cent of each in white vaseline or cold cream, was often helpful in removing or keep-

ing down the scaling and crusting over a considerable period in the very superficial type. If infiltration developed, or actual ulceration, it was probable that a malignant change had already developed, and the lesions were treated as basal-cell epithelioma.

Seborrheic Keratosis

Seborrheic keratoses, sometimes spoken of as senile flat wart or verruca seborrheica, were in general quite different. They were usually on covered parts of the body, such as the upper back, over the shoulders and over the chest. They were found, however, on the face, hands and abdomen. In general, these were sharply outlined, oval, slightly elevated, usually slightly pigmented and perhaps slightly greasy lesions. In certain persons there was often difficulty in distinguishing some of these lesions from the senile keratoses, but in general a distinction could be made. A definite hereditary factor was indicated by the fact that the lesions were seen in certain members of a family over two or three generations, or that such a history could be obtained.

In view of the fact that they seldom became malignant their removal was not necessary except for cosmetic reasons. They were destroyed in various ways as seemed necessary.

Eczema

Eczema and dermatitis are, of course, the most common diseases of any age group. It is a question whether there should be much distinction between cases of eczema and those of dermatitis. Both terms refer to an inflammatory reaction in the skin. The term "eczema," perhaps, will not disappear, but its use has decreased much in dermatology, and the term "dermatitis," either acute, subacute or chronic, has become more widely employed for simple inflammations of the skin, whether of external or internal origin. In this older age group the term eczema has been used for cases of inflammation of the skin that were not definitely due to an external contact, and in many cases no single factor could be assigned as a cause. The skin disturbance seemed more intractable than in younger persons, a fact that was particularly true when the lower legs were affected. We believed that there was often a circulatory factor, although not always associated with obvious varicosities. Many of these cases started with a pruritus or perhaps a mild dermatitis, with exaggeration thereafter by the trauma of scratching or rubbing, perhaps by low-grade secondary infection, sensitization to some therapeutic agent and stasis — that is, being on the feet too much for the circulatory system of the particular patient and so forth. Etiologic factors were often multiple. There were found in the cases in this group various degrees of itching and discomfort, and varying amounts of redness, swelling, excoriations, scaling, crusting, infiltration, pigmentation and so forth. Much patience was often required to obtain an account of the onset and course of the disease from these older people and their relatives, and to ascertain something of earlier treatments and the results of such therapy.

Recently Guy et al.* discussed geriatric nutritional eczema in patients past middle life with an eruption of the lower legs associated with varying degrees of edema. Hypoproteinemia was a main factor, and edema was abolished when an adequate supply of protein was given. These patients were usually amenable to a six-point plan of treatment: adequate mastication; a diet rich in proteins; administration of protein hydrolysates, concentrates and vitamins; correction of hypochromatic anemia; dilute hydrochloric acid with meals; and local care in keeping with the status of the inflammatory process. The additional factor of possible focal infection was brought out in the discussion of this report.

Treatment often had to be individualized, and careful, preferably written, directions given for the regime that was prescribed. Much time was often consumed in the details of treatment of acute, subacute and chronic types. Suffice it to say that soothing combinations, such as a modified calamine lotion and a zinc oxide or calamine, starch and vaseline ointment were usually prescribed at first. With much oozing and much redness and swelling, boric acid or weak potassium permanganate compresses were often well tolerated. Occasionally, an oil as a cleansing agent seemed preferable. In many cases in which the leg was affected it was essential that the patient keep off his feet, or wear a linen-mesh bandage properly applied.

A rather high percentage of these cases of contact dermatitis among older persons seemed to be associated with the soap that was used. There were a few cases due to nail polish, a few to plants, a few to nickel, and a few to paint solvent, and there were 1 or 2 cases of a large number of different agents with which the patient had been in contact. A great many of these cases involved the hands. Detection of the offending agent and its elimination were important for therapy but often difficult to achieve.

Pruritus

Pruritus was a very troublesome symptom. It is hardly necessary to emphasize the disastrous effect that a mild but persistent itch can have on the life and general condition of the older patient. And a severe pruritus, if unrelieved, will prevent the sleep the patient needs, interfere with appetite and general nutrition, depress him mentally and in general greatly affect the general health.

About 50 per cent of the cases were of the so-called senile type, with very few or no demonstrable skin lesions except for the excoriations produced in an attempt to relieve the itching by scratching. Of the remainder, localized perianal and vulval itching

*Guy, W. H., et al. Geriatric nutritional edema. *Arch. Dermat. & Syph.* 57:822-827, 1948.

formed the largest group. In many cases both areas were involved. Only 6 per cent of these cases were of diabetic origin. The diagnosis of pruritus particularly a generalized pruritus, called for a careful detailed examination to prove conclusively that there was no general causal factor. Such itching is, of course, associated with diabetes not infrequently, the lesions of the lymphoblastoma group, liver conditions and other diseases. In the same way, localized pruritus called for investigation, both for a local causal factor and for general factors. In the northern part of the country numerous cases of pruritus of the generalized type appear in older persons with the onset of cold weather and clear up in the spring — the "winter itch," or pruritus hiemalis. The neurogenic factor was a more difficult one to evaluate in both the general and the local type, but in cases of perianal, vulval and scrotal pruritus in which only the results of rubbing and scratching were apparent, with no other lesions to account for the itching, a neurogenic factor was given serious consideration.

Treatment of these cases was often difficult. It is imperative that all possible causal factors found on general examination be eliminated so far as practically possible. Frequently, in the general type, the kind of soap seemed important, and the use of a so-called superfatted soap or of less soap, or perhaps no soap at all, in bathing, followed by some mild emollient, often provided considerable relief. The treatment of the localized pruritic areas in older patients is often a severe test of the physician's therapeutic skill. Phenol is still the best single antipruritic agent, and menthol and camphor can be useful in treatment, but careful observation is required to be sure that these agents do not act as sensitizers. Whether some of the new antihistaminic agents will prove useful in these cases still remains to be proved. The itching was often an individual problem and can hardly be discussed in general without an individual case for consideration. Mild sedation was a helpful ally in many cases but was discontinued as soon as possible. Fractional x-ray therapy was used in carefully selected cases. It is to be deprecated that x-ray therapy has been employed to such a degree that numerous cases of atrophy and telangiectasia, with the resulting sequelae, appeared as the result of such radiation of localized pruritus. It is essential that a limit be set upon the amount of treatment to be given the individual area, and when that limit is reached the patient should be informed that his particular quota has been reached and it is inadvisable to continue further with such treatment. It is, of course, essential that every attempt be made to maintain accuracy of dosage if radiation is prescribed.

Discussion

Space does not permit the discussion of the other diseases noted in this series. In addition to the diseases mentioned above there were many diseases in which only 1 to 4 cases have been listed. Thus, there are many diseases of the skin with which the older patient can be afflicted and for which he will seek relief.

In the care of these patients it is well to remember that the older skin is drier and that less soap or perhaps a so-called super-fatted soap is frequently helpful. In addition, in colder weather the use of a thin oil or grease often gives considerable relief. Additional protection from cold weather gives relief in many cases, although wool seems to have an effect of producing itching in some.

In many older persons there was need to compromise with the usual directions given for the care of some skin diseases. There was the need to compromise with a strict diet if such diet seemed as if it would interfere with the daily routine of life that had been carried on over many years. Although it was essential to give very careful directions, perhaps in writing, it was necessary to compromise on some of the details to avoid complicating the life of the patient or family too much. Some of these patients were extremely meticulous, others very carefree, and others very forgetful, so that such directions varied with the individual patient. Relief of itching, especially of generalized itching, was of prime importance in many of these cases. Much consideration had to be given to procedures that were *essential* — treatment of skin cancer, remaining off the feet and so forth — as compared with measures not absolutely essential. In many cases improvement or relief was brought about by unusual methods or unacceptable proprietary applications, and it often seemed best to go along with such methods for a while without too sudden changes, with a gradual shift to methods and agents that should really have done better for the patient. It was often a difficult matter to decide whether to accept and go along with preconceived ideas or to attempt to alter them to a more generally accepted method. In other words, it was often especially necessary to treat the patient with the disease and in relation to his other diseases and not simply the cutaneous disease with which he was afflicted.

Summary

The case records of 2000 patients over sixty years of age with diseases of the skin are reviewed.

The most common diseases observed in this age group are discussed.

Fifty per cent of these patients received a diagnosis of one of five diseases, — senile keratosis, epithelioma, seborrheic keratosis, eczema or contact dermatitis, — and in 79 per cent the diagnosis was one of fifteen other diseases.

Senile keratosis and epithelioma — that is, premalignant and malignant disease — accounted for 28 per cent of the cases.

Women had a higher incidence of epithelioma and keratosis, as well as other diseases, and men a higher proportion of inflammatory diseases, such as eczema and contact dermatitis and fungous infection.

Relatively few unusual diseases were noted.

It is important that minor changes in the skin be examined early to prevent later extensive involvement, and that apparently insignificant growths be examined to determine if malignant lesions exist and to provide adequate therapy. The relief of itching and discomfort is quite important.

In older patients it is especially necessary that the patient as a whole, and not merely his cutaneous disturbance, be considered and treated.

REACTIONS FROM THE USE OF BENZODIOXANE (933 F) IN DIAGNOSIS OF PHEOCHROMOCYTOMA*

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PHEOCHROMOCYTOMA is a known cause of hypertension that is being more frequently diagnosed.[1] This tumor produces epinephrine or an epinephrine-like substance that is responsible for the observed increase in blood pressure. Pharmacologically the dioxane group of drugs (883 F, 933 F, 1164 F and others) prevent or reverse the hypertension produced by epinephrine in animal experiments.[2, 3] The compounds 883 F and 933 F do not have any significant effect on the blood pressure of dogs or rats with renal hypertension.[4, 5] Thus, the benzodioxane group of drugs would be expected to prevent the effects of circulating epinephrine produced by a pheochromocytoma, and thus to reduce blood pressure, but would be without effect in the patient with other forms of hypertension. Recently, a test for hypertension due to circulating epinephrine has been devised, on the basis of the adrenolytic effect of benzodioxane derivatives.[6]

The use of such drugs to block the effects of epinephrine will provide a more specific test in the diagnosis of pheochromocytoma. However, such agents as the benzodioxane derivatives can produce many side reactions that have not been sufficiently emphasized. The present paper reports the occurrence of severe side reactions resulting from the injection of a benzodioxane derivative in 2 patients with suspected pheochromocytomas.

METHOD OF ADMINISTRATION

The benzodioxane derivative used was 933 F (piperidino-methyl-benzodioxane). It was administered by the technic and in the dose utilized by Goldenberg, Snyder and Aranow.[6] The patient received an intravenous infusion of 5 per cent glucose, and with the infusion running control determinations of blood pressure were taken each minute for approximately twenty minutes. When the patient was adjusted to this procedure 933 F was injected into the infusion tubing for two or three minutes in a dose of 10 mg. per square meter of surface area.

CASE REPORTS

CASE 1. A 51-year-old woman was admitted to the hospital complaining of severe headaches, blurred vision, nervousness and weight loss. These symptoms had begun 3 years previously, with anorexia and headache. This was followed by a gradual onset of fatigability, attacks of dizziness, nervousness and palpitation. The headaches became worse, and 2 months before admission she complained of blurred vision and yellow spots before the eyes. The weight loss during this period was 36 pounds.

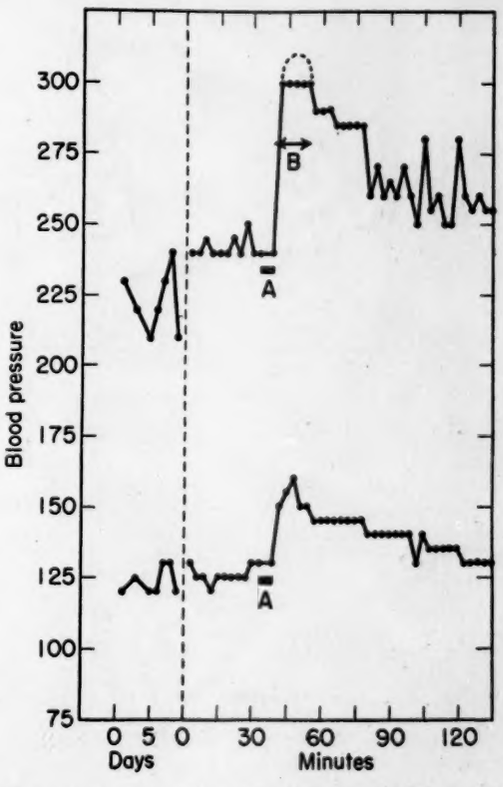

FIGURE 1. *Zero Time (Control Infusion Started). Injection of 933 F at* A. *Complaint of nausea and headache at* B.

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The past and family histories were noncontributory.

On physical examination the optic disks were blurred, and gray-yellow patches of exudate were present bilaterally. Arteriovenous nicking was marked, and several reddish-brown hemorrhages were present on the right. The heart was enlarged, with a diffuse apex thrust and a Grade II apical systolic murmur. Edema (Grade I) was present bilaterally in the legs and sacral region. The dorsalis-pedis pulses were strong.

The blood pressure was 225/130 (left arm with the patient recumbent), the pulse 92, and the respirations 16. The temperature was normal.

The right kidney was easily palpable and seemed to be lobulated. On x-ray examination the kidneys were of normal

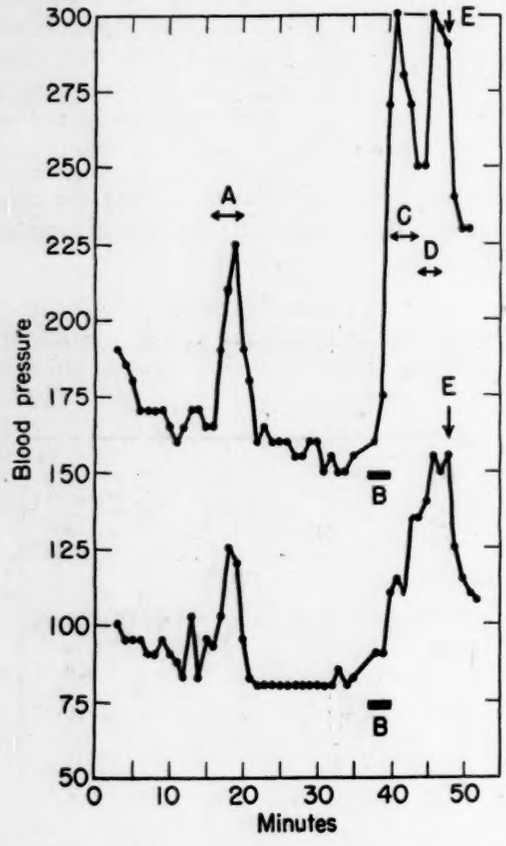

FIGURE 2. *Zero Time (Control Infusion Started).*

Spontaneous rise in blood pressure, with complaint of severe precordial pain at A. *Injection of 933 F at* B. *Patient complained of light-headedness and dizziness at* C. *Complaint of severe precordial pain at* D. *Administration of 15 mg. of morphine sulfate and 0.4 mg. of atropine sulfate at* E.

size and shape, the left being lower than the right. A suggestion of a triangular shadow was seen over each kidney, and the possibility of a left adrenal tumor was raised. Retrograde examination again revealed a lower left kidney, and just above the superior pole of the left kidney was a vague increase in soft-tissue density suggestive of a soft-tissue mass. Retrograde pyelography did not demonstrate abnormalities in the ureters or kidney pelvis, and dye excretion was normal. Further laminographic studies of the kidneys were indeterminate.

Although the clinical diagnosis was malignant hypertensive cardiovascular disease the possibility of a tumor of the left adrenal gland remained. For this reason piperidino-methyl-benzodioxane (933 F) was injected as a test for possible pheochromocytoma. A 5 per cent glucose infusion was administered, and with the infusion running, control blood-pressure readings were taken for 30 minutes (Fig. 1). At point *A* of Figure 1, 15.6 mg. of 933 F in 1.56 cc. of solution was injected into the infusion tubing over a 2-minute period. Immediately after the injection both the systolic and the diastolic blood pressure rose precipitately (Fig. 1). At point *B* of the graph the patient complained of nausea and headache. One and a half hours after the injection of 933 F the systolic blood pressure was still elevated, and the diastolic pressure had returned to normal. The pulse rate varied from 82 to 87 before the injection. After the injection of 933 F the pulse rate rose immediately to 98 for 2 minutes and then returned and stayed at the previous control range.

CASE 2. A 52-year-old woman was admitted to the hospital with the chief complaint of dizziness, tachycardia and anginal pain, which had suddenly begun 1 month previously, with pain radiating to the left shoulder and down the left arm. A trial of nitroglycerin therapy was without effect on the anginal attacks. The attacks increased in frequency, occurred 2 or 3 times per day, at any time of day or night, and were not related to exertion or meals.

The past and family histories were noncontributory.

Physical examination showed no dyspnea or cyanosis. The fundi were normal except for slight fullness of the veins. The left border of cardiac dullness was just outside the midclavicular line. The point of maximum impulse was in the fifth interspace 13 cm. from the midline. Normal sinus rhythm was present. A soft systolic murmur was present in the pulmonic area, and the aortic second sound was ringing in character. No other positive findings were obtained. The clinical impression was hypertensive cardiovascular disease, compensated on activity, with anginal syndrome and paroxysmal tachycardia of unknown etiology. The question of tumor of the adrenal medulla was raised.

The blood pressure was 190/110 (left arm) and 188/108 (right arm), the pulse 84, and the respirations 20.

The attacks of pain were observed in the hospital and consisted of severe chest pain, palpitation, sweating and flushing of the face and neck, rapidly followed by pain radiating down the left arm. During such an episode the pulse rate was 172 and regular, with a blood pressure of 278/148. One hour after the attack the blood pressure had decreased to 190/100. An electrocardiogram taken during one attack showed sinus tachycardia. In the hospital the blood pressure varied from 140/80 (pulse 70) to 300/160 (pulse 160). Plain films of the abdomen and laminograms did not reveal any masses, and the kidneys were of normal size and shape. Intravenous pyelograms were indeterminate.

A benzodioxane test was then performed. The patient received an intravenous infusion of saline solution, and control readings of blood pressure were taken for 37 minutes (Fig. 2). At point *A* of Figure 2 the blood pressure rose spontaneously, and she complained of severe precordial pain. The solid bar (*B*) indicates the injection of 18.0 mg. of 933 F in 1.8 cc. of solution into the infusion tubing over a period of 3 minutes. The blood pressure rose markedly after the injection (Fig. 2). At *C* the patient complained of a light-headed, dizzy feeling, and her face was flushed. This was closely followed by the complaint of lightheadedness and severe precordial pain (Fig. 2 *D*). At point *E* the patient received morphine sulfate (15 mg.) and atropine sulfate (0.4 mg.). The pulse rate rose from a control level of 60 or 70 to 140 for 5 minutes after the injection of 933 F.

Surgical exploration was subsequently performed, but no masses were found, and the adrenal gland was normal to palpation, which did not produce an increase in blood pressure.

DISCUSSION

In anesthetized animals, such as the dog, 933 F (2 piperidino-methyl-1, 4 benzodioxane) has only an adrenolytic effect when injected in small doses. With increasing doses of 933 F the pressor effect of injected epinephrine can be successively decreased, abolished and then reversed, producing now a fall in blood pressure. Higher doses of 933 F will have a sympatholytic action, and thus abolish the effect of sympathetic nerve stimulation.

In the nonanesthetized animal, with other reflexes remaining active, the injection of 933 F produces various side effects. Chief among these are central-nervous-system stimulation, hypertension

and tachycardia.[7] The hypertension and tachycardia caused by 933 F is a sympathomimetic effect that is not seen in the anesthetized animal. The effect of epinephrine on the heart rate is not abolished by 933 F; on the contrary the drug increases the tachycardia produced by epinephrine. Thus, side effects of this nature may be expected in some patients when 933 F and related compounds are used.

The effect of the benzodioxane derivatives in lowering the blood pressure of patients with pheochromocytoma[6] has been confirmed.[8] In such studies it was found that the usual response produced by 933 F in patients with essential hypertension was an increase in blood pressure.[6] Normal subjects also showed a rise in blood pressure after injections of 933 F, but less so in comparison with patients with essential hypertension. Other side reactions were noted, such as flushing, palpitation, nervousness, cold and clammy extremities, hyperpnea, mild headache, fright, sighing and dizziness. These reactions were seen chiefly when the injection of 933 F was made in thirty seconds and were noted much less with an injection time of two minutes.

In the 2 cases reported above, 933 F produced a marked rise in both systolic and diastolic blood pressure. That this is a central effect of the 933 F is seen by the simultaneous increase in pulse rate. Other side effects were nausea, headache, dizziness and flushing, and 1 patient complained of severe precordial pain.

The central-nervous-system stimulation caused by 933 F, as reflected in the marked increase in blood pressure and the tachycardia, is a dangerous side reaction, and is an inherent property of such compounds that apparently becomes more manifest in patients with hypertension that is not due to pheochromocytomas. A different type of adrenolytic drug, dibenamine hydrochloride, that may also stimulate the central nervous system has recently been reported. The use of dibenamine in the diagnosis of a case of pheochromocytoma has recently been described.[9]

Summary

An adrenolytic drug, 933 F (2-piperidino-methyl-1, 4 benzodioxane), was administered to 2 patients with suspected pheochromocytomas.

The injection of 933 F produced an immediate and marked rise in systolic and diastolic blood pressure, and 1 patient complained of severe precordial pain. The possible toxic effects of such compounds are discussed.

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MEDICAL PROGRESS

THE BIOCHEMISTRY AND CLINICAL APPLICATION OF VITAMIN P*

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THE term vitamin P was proposed by Armentano and his co-workers[1] to denote a group of compounds distinct from ascorbic acid that maintained the physical strength of capillaries. This concept grew out of investigations to determine why crude sources of vitamin C controlled hemorrhages in vascular purpura whereas purified ascorbic acid was ineffective. From the ascorbic-acid-free residue of the mother substance, a faintly yellow crystalline material, which was found to exert the so-called vitamin P activity, was extracted. Because of its derivation from citrus fruits, this active powder was called citrin. Various analyses revealed that citrin was a mixture of different flavones, and several of these were subsequently isolated.[2] Their potency has been the subject of considerable debate. Opinions also differ concerning whether these compounds actually function as vitamins. The original claims[3, 4] that vitamin P prolonged the lives and reduced the severity of the symptoms of scorbutic guinea pigs failed to stand up to independent investigation,[5, 6] and even Szent-Györgyi[7] could not confirm the initial results.

Early investigations were hampered by the difficulty of preparing a diet completely free of flavones. In addition, because of the similar natural distribution of flavones and ascorbic acid, diets that excluded sources of flavones were also deficient in vitamin C. Animals maintained on such regimes developed scurvy, which masked possible effects of vitamin P deficiency. It remained for Zacho[8] to achieve a pure vitamin P deficiency state in his animals by adding pure ascorbic acid to their flavone-free diet. The only abnormality that developed in such animals was a capillary weakness, which responded specifically to vitamin P. This claim has been well substantiated.[9, 10] Scarborough[11, 12] has described a vitamin P deficiency in human beings characterized by capillary weakness, spontaneous perifollicular hemorrhages and rheumatic pains in the legs and shoulders. Again, a specific, rapid response to vitamin P was claimed, whereas ascorbic acid was ineffective. Although Scarborough's work seemed to be well controlled, his findings could not be confirmed by Lazarus and his co-workers,[13] who maintained that neither vitamin P nor ascorbic acid remedied the capillary weakness in scurvy. From this welter of conflicting evidence, it is impossible to arrive at any definite conclusions. Possibly, the use of injectable preparations might lead to more uniform results.

Regardless of their acceptance as vitamins, the flavones have attained an important position in clinical medicine because they appear to exert a nonspecific, stabilizing effect on capillaries. This applies to a wide variety of pathologic conditions in which capillary defects are present. In addition, as pointed out below, evidence that vitamin P stabilizes ground substance opens new avenues of investigation into the relation between vitamin P and the numerous diseases to which ground substance falls prey.

When capillaries that are subjected to physical stresses rupture excessively and form petechiae, they are said to display increased fragility or decreased resistance. The physical stresses are either an increased intracapillary pressure obtained by the application of a blood-pressure cuff to the upper arm or a negative external pressure obtained by the application of a suction cup to the skin.

These tests have recently been reviewed in detail.[14] The numerous modifications to which they have been subjected clearly indicates that they leave much to be desired. There is no correlation between positive and negative pressure. When performed at the same time the tests may yield entirely divergent results.[13] Influences on capillary resistance due to age,[15] sex,[16] season, time of day, emotions,[17] trauma[18] and hemorrhage, render the interpretation of these tests most difficult. The confusion has been compounded by the failure of many investigators to heed the warning[19] that tests repeated at intervals of less than three weeks may yield false-negative results.

The term "increased capillary permeability" is also used loosely to indicate a weakness of capillary walls. Capillary permeability is gauged by the extent of transudation following venous stasis[1] or by the degree and rate of streamer formation following the intradermal injection of the dye patent blue.[20] In contrast to the fragility measurements, the permeability tests have had a limited application.

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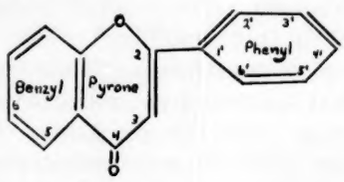
Definition

Until recently, the only abnormality detectable in laboratory animals deficient in vitamin P was an increased capillary fragility, and substances that could correct this abnormality were described as having vitamin P activity. The term has acquired a broader meaning and is used to describe agents that increase the strength of capillaries of normal animals. Because of the unreliability of tests of capillary strength, other procedures have been suggested to demonstrate vitamin P activity. Thus, pulmonary hemorrhages have been produced in mice by sudden reduction in atmospheric pressure. It has been claimed by some [21] but denied by others[22] that vitamin P reduces the severity of this type of hemorrhage. Other suggested bases for biologic assay are the reduction in bleeding time in normal guinea pigs[23] and the increased resistance of erythrocytes to hypotonic saline solution,[24] both of which are effected by vitamin P. It is obvious, then, that the term vitamin P has exceeded the usual limits that one associates with the word "vitamin."

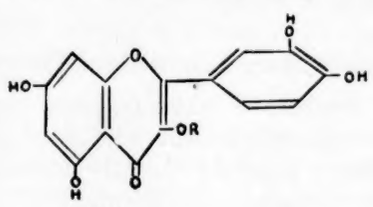
Chemistry

The many types of vitamin P have a similar structure. They may all be regarded as derivatives of flavone proper (phenyl gamma benzo pyrone) or its variations[25, 26]:



Flavone

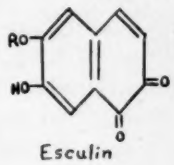
When the double bond between carbon atoms 2 and 3 is saturated, the compounds are called flavonones, examples of which are hesperidin and eriodictin (eriodictyol). When a hydroxyl group is attached to the third carbon atom, the structure is known as a flavonol, of which rutin is representative. Derivatives of these three variants of the flavone nucleus are collectively referred to as flavones. Rutin, for example, is the rhamnoglucoside of 3, 5, 7, 3′, 4′ pentahydroxy flavone:



Rutin

Flavones

The flavones are a group of yellow, plant dyestuffs that are widely distributed in nature, being found in citrus fruits, tobacco plants and buckwheat. The last is the present commercial source of rutin. The existence of the flavones was known long before their vitamin P activity was appreciated. Hesperidin, for example, was discovered in 1828.[2] More recently isolated types of vitamin P are the flavins[27] and coumarins,[28] represented by *d*-epicatechin and esculin respectively. In the former, the ketone group on the fourth carbon atom of the flavone nucleus is reduced, and the double bond between the second and third carbon atoms is saturated. The coumarins show the greatest divergence from the flavone nucleus. The phenyl ring is lacking, the pyrone ring is reduced, a double bond lies between the first and second carbon atoms, and ketone groups are attached to the third and fourth carbon atoms:



Esculin

D-epicatechin and esculin are among the most potent types of vitamin P, having an activity at least five hundred times that of citrin. Catechins are extracted from vegetables and kola nuts, and esculin is derived from chestnuts.

Identification of Vitamin P Compounds

Spectrographic analysis is the only certain method for the identification of individual vitamin P compounds. Various colorimetric procedures are available but they are all group specific.[27, 29, 30] Since not all flavones or catechins are endowed with vitamin P activity, the results of colorimetric procedures need not be synonymous with vitamin activity.

Metabolism

Very little is known of the fate of vitamin P after its ingestion. The little information available deals only with the soluble type of compound. As yet no one has traced the pathway of insoluble compounds like rutin given by mouth. When soluble compounds are injected parenterally, a variable portion may be recovered in the urine and bile for a period extending over several hours or days.[31, 32] The amount excreted depends, in part, on the previous body store of vitamin P. Other factors that govern excretion, the fate of the unrecovered fractions and the intermediary metabolism in the body have all to be worked out.

Pharmacology of Vitamin P

Different types of vitamin P have different pharmacologic properties.[33] Some, like eriodictyol, are inert when injected intravenously. Others, like

quercitrin and quercetin derivatives of rutin, produce a depressor response attributed to arteriolar dilatation. Intravenous administration of rutin itself has little or no effect on the blood pressure of cats[34] and dogs.[35]

The catechins are unique in their ability to stimulate capillary vasomotion.[34]

All types of vitamin P inhibit the oxidative destruction of epinephrine.[33] Some of them also partly simulate the action of that substance. For example, rutin and its aglycone, quercetin, both relax the guinea-pig colon.[33]

Toxicity

The only evidence of possible toxic manifestations of vitamin P is the depressor response that dogs exhibited after the intravenous injection of some of these compounds, and the depressor response that a patient with malignant hypertension experienced when 300 mg. of hesperidin methyl chalcone was injected intravenously.[31] The latter compound has been administered to human beings in oral doses up to 15 gm. without any detectable adverse effects. Solutions of rutin have been injected in animals in amounts up to 500 mg. per kilogram of body weight without any evident acute toxicity.[36] Rats fed diets containing naringin, hesperidin or rutin in amounts up to 1 per cent for as long as two hundred days did not show any signs of toxicity. On histologic examinations of the organs of the rats fed hesperidin and rutin, the tissues appeared normal.[37] Rutin in doses up to 500 mg. daily has been administered to human beings orally, and no toxic signs could be ascribed to this therapy.[38]

Evidence suggests that vitamin P, in addition to being free of toxic characteristics, reduces the toxicity of protoplasmic poisons such as heavy metals[39] and thiocyanates.[19]

Mechanism of Action

Capillary-Vasomotion Theory

The mechanism of the regulation of capillary resistance and permeability by vitamin P is, as yet, poorly understood. The first theory, proposed by Parrot and Lavollay,[40] was that vitamin P substances affected the capillaries indirectly by inhibiting the oxidative destruction of circulating epinephrine. The authors found that flavones inhibited the oxidation of epinephrine in vitro and that they prolonged the action of epinephrine on the colon and seminal vesicles of the guinea pig.[34] The claim that the flavones had no direct action on the guinea-pig viscera was subsequently disproved, but the epinephrine-sparing action of vitamin P has been substantiated.[33]

Adrenochrome Theory

The epinephrine theory was modified[40] when it was found that a latent period of ten to thirty minutes elapsed before a rise in capillary strength could be detected after the injection of this hormone into guinea pigs and human beings. This was in contrast to the usual promptness of the classic action of epinephrine, and it was postulated that the capillary changes were mediated by one of the early products of epinephrine metabolism, such as adrenochrome. This viewpoint was strengthened by the findings that various nonpressor adrenochromes[41] increased capillary resistance in normal human beings and normal and scorbutic guinea pigs. Although the capillary-vasomotion theory was thus rejected, it was recently revived by others,[34] who found that the catechins markedly stimulated capillary contractions. However, this theory still appears to be untenable since purified *d*-catechin, which stimulated capillary contractions, was, in the hands of others, shown to be devoid of vitamin P activity.

The adrenochrome theory was later expanded to include histamine as its chemical antagonist. This seemed plausible, particularly when antihistaminics were found to increase capillary resistance. Scorbutic guinea pigs demonstrated an increased sensitivity to histamine that could be restored to normal by vitamin P. However, in normal animals, vitamin P failed to neutralize the effects of histamine on the intact animal or the isolated colon. Thus, it was concluded that vitamin P did not directly antagonize histamine but that it reacted with the tissues so as to prevent histamine from increasing their permeability.[42] The failure of vitamin P to demonstrate antihistamine activity in the normal animal does not correspond with the increase in capillary resistance observed in normal persons after the administration of vitamin P or adrenochrome. This casts considerable doubt on the histamine aspect of the theory, as does the observation that histamine is not a physiologic regulator of capillary permeability.[43] The increased susceptibility of vitamin P deficient animals to histamine is probably a reflection of a generalized nonspecific increase in tissue permeability that these animals acquire. In such animals, even an inert substance such as saline solution, when injected intradermally, diffuses more extensively than normally.[44] If a physiologic antagonist of vitamin P does exist, a more likely suggestion is hyaluronidase.[45]

Epinephrine-Pituitary-Target-Gland Theory

Another mechanism has suggested itself on the basis of the epinephrine-sparing action of vitamin P. This theory suggests that the ultimate factors acting on the tissues are the hormones of the adrenal cortex and, possibly, the parathyroid glands. It is known that epinephrine causes a discharge of the anterior pituitary gland that, in turn, leads to an increased output from the various target glands.[46] The adrenocortical hormones have been shown to

increase the strength of capillaries,[47] and the parathyroid hormone to increase the resistance of the connective tissue.[48] Thus, vitamin P is visualized as regulating capillary resistance by an endocrine mechanism based on the ability of epinephrine to mobilize the pituitary gland and its target glands. It is not yet known whether adrenochromes can emulate this action of epinephrine on the endocrine system. Since adrenochromes are devoid of most of the properties that limit the administration of epinephrine, such information might be of considerable practical as well as academic interest.

The Direct-Action Theory

A theory commendable for its simplicity is that of Lenaz and Albori.[49] It was based on their finding that blocks of agar in citrin solution absorbed considerably less fluid than those in a control medium. The results were interpreted according to the postulate of Gellhorn that colloid hydrophilia was a function of colloid permeability. Since citrin decreased the hydrophilia of the agar blocks, it was concluded that it had done so by reducing the permeability of this colloidal material.

In conclusion, it is apparent that little is known about the mechanism of action of vitamin P. These substances are administered, and the end results observed. There is a vast gap in knowledge concerning what transpires between these two points.

The Clinical Significance and Vitamin P Therapy of Capillary-Fragility States

Several types of vitamin P have been employed in diseases in which capillary weakness has been demonstrated or suspected. By controlling the capillary factor with vitamin P it has been possible at times to arrest a train of events that, if uninterrupted, would have imposed a serious burden upon the patient. The significance of the capillary weakness and results of vitamin P therapy are discussed below.

Allergic States

An increased capillary fragility has been found in allergy; this weakness and the vascular derangements, such as angioneurotic edema[50] and allergic purpura,[51, 52] have responded favorably to vitamin P therapy. No information is available on the nonvascular aspects of allergy in human beings. A report by Rapaport and Klein[53] on the value of vitamin P in correcting capillary fragility in allergic children makes no mention of the effects of vitamin P, if any, on the allergic diseases from which these children suffered.

Animal studies indicate that pretreatment with vitamin P fails to inhibit the acquisition of the hypersensitive state,[35] and most observers agree that it does not suppress the antigen-antibody reaction.[35, 54] The claims that vitamin P prevents anaphylactic death in normal animals[55] have not been substantiated. However, it appears that vitamin P does stabilize certain peripheral substrates against the action of metabolites released during the antigen-antibody reaction. Thus, vitamin P could partially offset the action of histamine when the capillary wall was the substrate.[56] When smooth muscle of bowel, bronchus or vascular tree was the effector organ, no antihistamine power could be demonstrated.[33, 35, 36] Even with relatively tremendous doses of rutin, no antihistamine activity could be elicited in intact rabbits when the effector organ was the smooth muscle of the pulmonary-artery tree.[36] In summary, it is generally agreed that there is a capillary weakness in allergic states that may be corrected by vitamin P. The cause of the capillary dysfunction is unknown. Possibly, the weakness is due to excessive activity of trypsin, which is said to be capable of digesting interendothelial cement.[57]

Natural Hemorrhagic Diathesis

Although coagulation disturbances are generally considered to be the prime cause of bleeding in conditions such as thrombopenic purpura, leukemia and aplastic anemia, Roskam,[58] in 1921, and subsequently others[59] have regarded the platelet factor as secondary in importance to a capillary defect. Even in hemophilia,[60] it has been suggested that a capillary disturbance may be of importance as well as the hypocoagulability of the blood. In animals, experimental thrombopenia fails to produce bleeding. Capillary damage must also be present.[61] After splenectomy in thrombopenic purpura, it has been claimed that cessation of bleeding paralleled recovery from the capillary defect more closely than restoration of the platelet count.[61] McFarlane[62] has shed some light on the nature of the capillary factor. He has described structural changes in capillaries of adults suffering from vascular and thrombocytopenic purpura. In normal persons closure of capillaries was found to be an important factor in arresting capillary bleeding. In the above conditions, post-traumatic capillary closure failed to occur. It would be of interest to know if this capillary contractility returned after splenectomy, but no mention was made of this.

In vascular purpura[1] and hereditary hemorrhagic telangiectasia,[63] vitamin P has been able to arrest bleeding. In these conditions a simple mechanical weakness seems to operate, and may be reinforced by vitamin P. In thrombocytopenic purpura,[1, 64] in which a multiplicity of factors are involved, vitamin P has proved to be of no value. The compounds used so far do not stimulate capillary contractions. In view of McFarlane's findings of capillary atony, it would be interesting to try the catechins in this disease since they strongly stimu-

late capillary vasomotion. In a single case of hemophilia, Raunert[65] claimed that two intravenous injections of citrin given several hours apart were followed within twenty-four hours by cessation of bleeding, whereas the usual measures had been ineffective over a four-week period. However, as in all cases in which multiple therapy is given, the question of which agent produced the clinical response is problematic.

Radiation Disease

Over a period of years, it has become evident that hemorrhage following radiation may be due to at least three factors: thrombopenia,[66] capillary damage[67] and the presence of a heparinoid substance in the circulation.[66] The role of thrombopenia has been discounted because bleeding does not necessarily coincide with reduction in platelet counts.[66]

Mathewson[68] was the first to use vitamin P for the control of radiation hemorrhage. Severe retinal hemorrhages developed in a patient receiving irradiation by spray technic for multiple myeloma. After vitamin P therapy the retinal bleeding stopped, as did hemorrhages from the nose and bladder, the latter antedating the x-ray therapy. Bleeding recurred when vitamin P was withdrawn and stopped again when the vitamin therapy was resumed. Mathewson stressed the importance of the capillary factor in x-ray therapy and suggested the prophylactic use of vitamin P to reduce the danger of hemorrhage from this type of treatment. Experimental confirmation of this suggestion has been brought forth by Reckers and Field.[69] Fifty dogs were subjected to a single exposure of 350 r. Twenty-five served as controls, and of these, 16 (64 per cent) died in thirteen to thirty days. All 16, as well as 3 of the survivors, showed widespread hemorrhagic phenomena. The other 25 dogs were treated with rutin orally, 50 mg. three times a day beginning one week before radiation. Of this treated group, only 3 (12 per cent) died. All the survivors of the rutinized group, as well as 1 of the 3 that died, were relatively free of petechiae and ecchymoses during the post-radiation period, and when autopsied at forty to sixty days. In addition, several rutinized dogs survived a severe leukopenia lasting from ten to fourteen days. The authors stated that in their previous experience, spontaneous recovery from severe radiation leukopenia of this duration was extremely rare. In mice[70] rutin failed to prevent death from radiation, but it must be noted that, in this species,[71] hemorrhages are frequently difficult to find and are not an important cause of death. It therefore seems that the protective action of rutin, as in other instances, is largely confined to the vascular tree.

After the explosion of atomic bombs, three types of energy are liberated: blast, heat radiation and ionizing radiation.[72] The last is said to induce pathologic changes identical to those resulting from overdosage of irradiation. At Hiroshima and Nagasaki,[73] the exposed persons who survived the blast and heat effects developed an illness similar to that which Shouse and his co-workers[74] and Reckers et al.[69] had produced in dogs with overdosage of x-rays. All the formed blood elements were reduced, mostly owing to destruction of bone marrow. Terminally, petechiae appeared in the skin, and blood oozed from the body orifices. At autopsy, hemorrhages were found in the tissues and viscera, including the brain, meninges, kidneys and gastrointestinal tract.[75] Of the 125,000 deaths resulting from the atomic explosions it has been estimated that from 8 to 20 per cent were due exclusively to radiation effects.[72] In view of the importance of hemorrhages as a cause of death in these cases, the ability of rutin to inhibit radiation-induced bleeding is of obvious significance. In addition, it has been shown that rutin accelerates the recovery of tissues burned by overdosage of x-ray.[76] Several investigators[75] found that the degenerated bone marrow of many of the survivors retained a regenerative capacity, and they stated that if advantage had been taken of this feature, the death rate from ionizing radiation would have been much lower. These findings suggest a possible prophylactic value of vitamin P in persons subjected to ionizing radiation for therapeutic or other purposes. The findings are of such potential significance that ample confirmation of these observations is eagerly awaited.

Dicumarol Therapy

The occurrence of hemorrhage after administration of Dicumarol does not necessarily parallel the prolongation of the prothrombin time. Bleeding has occurred with only moderate depression of prothrombin activity, and conversely, when the prothrombin has been excessively prolonged, expected hemorrhages have frequently failed to materialize. For this reason, factors other than hypocoagulability of the blood have been sought that might have a bearing on bleeding. Wright and Prandoni[77] have shown that, even when Dicumarol produces hemorrhage, there is no increase in capillary fragility. However, in dogs given Dicumarol, Bingham, Meyer and Pohle[78] found marked dilatation of capillaries, small arteries and veins. This suggested a vascular component for the institution of bleeding—a viewpoint that has been stressed by Quick.[79] McLean and Brambel[80] gave rutin to patients receiving Dicumarol, but since none of the controls bled, the effects of rutin could not be judged. Clark[81] administered sufficient Dicumarol to rats to induce bleeding and found that rutin given orally failed to prevent the hemorrhages. Since in these experiments the rats may have succumbed before

the latent period of rutin activity expired, Levitan and Schwager[82] carried out similar experiments in rabbits, using esculin, which is a potent, quick-acting type of vitamin P. Like rutin, esculin failed to prevent the hemorrhages. Neither rutin nor esculin produces capillary contractions. In view of the pathological evidence of vascular engorgement in Dicumarol poisoning, it would be of interest to test the catechins in this condition since they are said to stimulate vasomotor activity.

Degenerative Vascular Disease

As arteries degenerate, newly formed capillaries appear about the atheromatous plaques in the intima.[83] These intimal capillaries[84] are distinct from the vasa vasorum, which lie in the outer half of the artery wall, and appear only after arteriosclerosis has progressed to a moderate degree. Their role in the pathogenesis of coronary and cerebral thrombosis has been established by Paterson[84] and confirmed by others.[85] When the capillaries rupture, an intimal hemorrhage that leads to the development of a thrombus in the adjacent lumen is formed. The suggestion that a similar mechanism operates in cerebral hemorrhage[86] apparently stimulated Griffith and Lindauer[19, 38] to study the role of capillary fragility in cerebral and retinal hemorrhages complicating hypertension. They confirmed Levrat's[87] finding that the incidence of such complications was considerably greater when an increased capillary fragility was present. Numerous studies since 1872[88, 89] have shown that capillaries deteriorate in arteriosclerosis, and hence the finding of an increased fragility in such circumstances reflects a diffuse vascular degeneration. The correlation between positive fragility tests and a high incidence of vascular accidents thus becomes apparent. Griffith and Lindauer[38] claimed that they could correct the capillary weakness in 75 per cent of such cases by the use of rutin, and concomitantly, the incidence of cerebral and retinal hemorrhages was reduced. Unfortunately their control group consisted of the 25 per cent whose capillary defect failed to respond to rutin, because of either insufficient or intermittent dosage. This choice of a control group complicates an evaluation of their findings. Other investigators,[90] in smaller series of cases and over relatively short periods of observation, have obtained varied results. Final conclusions regarding the effects of rutin on the vascular complications of hypertension cannot be made from the data available at the present time.

Diabetes Mellitus

Numerous workers have found a high incidence of increased capillary fragility in this disease, particularly when retinopathy is present.[91, 92] This is partly due to the premature development of arteriosclerosis. The retinopathy, however, depends on factors in addition to arteriosclerosis. Changes in plasma proteins that were more pronounced in cases complicated by retinopathy have been found.[93] An endocapillary layer of protein has been described by Danielli[94] as an integral part of the capillary wall that regulates pore diameter. A disturbance of this layer secondary to the changes in plasma proteins might contribute to the retinopathy by increasing the size of the pores so as to allow the escape of blood constituents that go to form the hyaline plaques.

Several types of vitamin P have been used to control the retinopathy. The results have not been dramatic.[1, 91, 92] Objective improvement has not been attained, but it appears that the degenerative process has been arrested in patients whose capillary fragility returned to normal. According to Rodriguez and Root,[91] this may not be achieved until many months of intensive therapy have elapsed. It appears, then, that little can be expected from vitamin P therapy in diabetic retinopathy unless large doses are administered indefinitely.

Frostbite

The capillary damage that occurs in this condition prompted Fuhrman and Crismon[95] to study the effects of rutin in frostbite. Large doses of rutin administered to rabbits prior to or shortly after the extremities were subjected to low temperatures markedly reduced the extent of subsequent gangrene. However, these effects of rutin were not reproducible when the ears were the test object.

Albuminuric Diseases

Dunn[96] states that Cohnheim originated the idea that damage to peripheral capillaries was important in the development of renal edema. Some support for this concept is afforded by the findings of Göthlin[97] that capillary resistance is decreased in albuminuric conditions. Although the cause of this change is unknown, two possibilities are present. Glomerulonephritis and its variant, lipoid nephrosis, are believed by many to develop on the basis of an acquired sensitivity to streptococcal toxin, and as was previously shown, capillary fragility is increased in allergic conditions. Thus, an increased capillary fragility and permeability of an allergic nature may explain the early formation of edema, before plasma proteins are significantly reduced. The loss of albumin through visibly damaged glomeruli might also contribute to the capillary damage by disrupting the endocapillary layer.

Several authors have used vitamin P in various nephritides. Again the results are contradictory.[1, 98, 99] Further work is required, particularly with injectable preparations.

Dermatologic Conditions

Goldfarb[100] has used citrin therapy in psoriasis, based on Wertheim's description of morphologic capillary alterations in this disease. Of 45 patients treated 30 were said to have improved on the basis of diminution in the infiltration of the lesions and a decrease in scaling. In only 2 patients did the lesions completely disappear. In a variety of dermatologic conditions, crude hesperidin and hesperidin methyl chalcone administered for ten days to three weeks have proved to be of little value.[101]

Miscellaneous

Several reports have appeared on the use of rutin in bleeding of obscure origin. Schwager[52] administered rutin, 20 mg. three times a day, to a five-year-old girl with a history of epistaxis recurring three to six times weekly for several months. The only abnormal finding was an increased capillary fragility. After a month of rutin therapy, the capillary strength became normal, and the bleeding stopped. During an eighteen-month follow-up period, only one nosebleed occurred, in the course of an upper-respiratory-tract infection. Shanno[64] reported 2 cases of hemoptysis, and Zfass[102] 1 case of hematemesis of obscure etiology that responded favorably to rutin. In both reports the capillaries were excessively fragile prior to rutin therapy.

Fields for Future Study

In spite of the widespread application of vitamin P, there remain several commonly occurring diseases in which it has yet to be applied. These include schizophrenia, cryptogenic epilepsy, migraine and Ménière's syndrome, in all of which capillary disorders appear to be of importance.

Capillary microscopy has revealed bizarre morphologic abnormalities in schizophrenia, and the weakness of these vessels is borne out by their directly observed tendency to rupture spontaneously.[103] An increased capillary permeability has also been detected by the technic of blister formation.[104] The possibility that recurring episodes of petechial hemorrhages in the brain substance contribute to the mental deterioration and the possible interruption of this process by vitamin P makes interesting speculation.

In cryptogenic[105] and deteriorated types[106] of epilepsy and in migraine,[105] which is genetically related to epilepsy, structural abnormalities of capillaries have been described. During attacks of migraine an actual increase in capillary permeability has been observed,[107] as indicated by blurring of capillary outlines. Similar changes have occurred premenstrually,[107] at which time migraine attacks are prone to occur. Migraine is frequently precipitated by emotional conflict, which is also said to increase capillary fragility. These considerations, as well as the claim that vitamin P prevents the increased fragility that occurs in emotional stress,[17] suggest a trial of vitamin P therapy in these diseases.

In Ménière's disease,[108] edema of the labyrinth has been implicated, and in view of the probable capillary basis for the edema, this syndrome merits a trial of vitamin P therapy.

The more recently discovered types of vitamin P, such as the catechins and esculin, also deserve further clinical application particularly in view of their potency, moderate solubility in water and rapid absorption from the gastrointestinal tract. Both may be given parenterally in aqueous solution. Rutin, the current popular type of vitamin P, is practically insoluble in water and must be dissolved in alkali alcohol, pyridine or propylene glycol for parenteral use. Clinically, rutin has been given only by mouth. Its absorption and excretion have not as yet been studied, and except for clinical response, there is no proof that it is absorbed from the gastrointestinal tract. Although it is possible that the long latent period observed in the clinical use of rutin is due to the nature of the pathologic condition being treated, it may also be referable to poor absorption from the intestines. Further work is required to clarify this point. The capillary vasomotor stimulation that the catechins alone exhibit[34] suggests their application in diseases such as thrombocytopenic purpura in which capillary atony is said to be an important factor in the genesis of bleeding.[62]

Although almost all the investigations carried out to date are concerned with capillaries, recent evidence suggests that vitamin P is concerned with the stability of the system of ground substance of which that present in capillaries is only a small part. The ability of spreading factors to increase the permeability of connective-tissue ground substance has been reduced by vitamin P[44, 109] and enhanced by anti-vitamin-P factor.[44] The significance of this observation lies in the number of diseases to which ground substance falls prey. Abundant data have been accumulated[110] indicating that the spread of infections and malignant growths is partly determined by the degree of permeability of ground substance. The stabilizing effect of vitamin P[44, 109] is thus of obvious significance. Ground substance is probably present in the erythrocyte membrane, and its stabilization by vitamin P is suggested by the increased resistance that erythrocytes treated with vitamin P demonstrate when exposed to hypotonic saline solution.[24] This observation raises the problem of a possible relation between vitamin P and hemolytic and aging processes of the red blood cell. Ground substance is present in the artery wall,[89, 111] and in experimental arteriosclerosis it has been

clearly shown that alteration or damage of this ground substance takes place before lipoids are deposited in it.[112] That vitamin P stabilizes arterial ground substance is suggested by the claims that rutin reduces the incidence of cerebral hemorrhage in hypertension.[38] Although this study was undertaken on the assumption that intramural capillary hemorrhage might determine the occurrence of cerebral hemorrhage, such a mechanism has never been clearly demonstrated in this type of vascular accident. It is generally believed that cerebral hemorrhage is due to an elevated arterial pressure rupturing the entire thickness of a weakened vessel wall. Since little or no change in blood pressure has been observed in such cases treated with rutin, the beneficial effects appear to be due to local stabilization of the vessel wall. With these considerations in mind, I attempted to study the effects of rutin on the prevention of experimental arteriosclerosis in rabbits. Uncontrollable factors twice reduced the number of surviving animals so as to preclude definite conclusions, but some protection seemed to be afforded by rutin. There is ground substance present in intervertebral disks, probably hyaluronic acid.[113] The interesting hypothesis has been advanced that disk degeneration is due to disease of the ground substance of the disk and, as such, reflects a widespread ground-substance degeneration, possibly owing to repeated infections caused by hyaluronidase-producing organisms.[114] If this is true, the ability of vitamin P to stabilize ground substance against the action of hyaluronidase[44, 109] is again of obvious importance.

Increasing attention is now being directed to the role of mucus in the prevention of peptic ulcer and chronic ulcerative colitis. Meyer and his coworkers[115, 116] have shown that the enzyme lysozyme, which is capable of digesting mucus, is present in high concentration in the gastric juice of patients with peptic ulcer and in the stools of patients with chronic ulcerative colitis. They have suggested that dissolution of the mucin coating by lysozyme activity exposes the bare gastrointestinal mucosa to the eroding action of hydrochloric acid and indigenous bacteria. The protective action that gastric mucin affords the gastric mucous membrane has been clearly demonstrated. The mucoitin sulfuric acid of gastric mucin is closely related to the hyaluronic acid and chondroitin sulfuric acid of connective-tissue ground substance.[113] The ability of vitamin P to stabilize the ground substance raises the question whether a similar effect might be exerted on gastrointestinal mucin. In this connection, it may be more than coincidental that cabbage juice, which has been claimed to accelerate the healing of peptic ulcer,[117] is a rich natural source of vitamin P. Other conditions that suggest themselves for vitamin P studies are the collagen diseases and amyloidosis.

In conclusion, vitamin P studies have been made in numerous diseases in which capillary defects appear to play a role. The purpose of this paper is to review these findings and to direct attention first to other diseases in which capillary factors appear to be of importance and secondly to diseases of ground substance that might provide interesting material for future vitamin P investigation.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 35461

PRESENTATION OF CASE

A sixty-three-year-old laborer entered the hospital complaining of epigastric pain.

He had been well until eight years before admission, when he developed burning epigastric pain. There was no relation to meals. His physician prescribed a "white stuff," which relieved the pain but caused constipation. A gastrointestinal series at that time was negative. The pain disappeared after a few weeks and did not return until two years later, when there was a similar attack. The third episode occurred six months before admission. The pain usually came on when he was hungry, beginning in the midepigastrium and radiating toward both flanks. It occurred daily, one to four hours after meals, and was relieved by food, milk and the white medicine. His worst attack began three weeks before admission; the pain was more severe than ever, but was still relieved by food and sometimes by the passage of flatus. There had been no nausea, vomiting, change in bowel habit, melena or grossly bloody stools. There had been little weight loss, the weight on admission being 165 pounds; one year previously, it had been 170 pounds.

Physical examination revealed a well developed and well nourished, muscular man in no discomfort. The anteroposterior diameter of the chest was increased. The lung fields were hyperresonant. The heart was normal. There was slight tenderness without spasm in the midepigastrium. The costovertebral angles were slightly tender. No masses other than what appeared to be feces in the colon were palpable.

The temperature was 99°F., the pulse 74 and the respirations 20. The blood pressure was 138 systolic, 78 diastolic.

Laboratory studies revealed a red-cell count of 5,000,000, with 14 gm. of hemoglobin, and a white-cell count of 9600, with a normal differential count. Urinalysis was normal. The total protein was 7.4 gm., the nonprotein nitrogen 29 mg., and the fasting blood sugar 81 mg. per 100 cc. A stool was guaiac negative.

A gastrointestinal series revealed a deeply penetrating ulcer in the midportion of the posterior wall approaching the greater curvature. It measured 2 cm. in width and 3 cm. in depth. About the ulcer there appeared to be a good deal of soft-tissue swelling. Barium passed the pylorus without hesitancy, filling the duodenal bulb to its normal contour.

A gastroscope was introduced, and normal, rather active peristaltic waves were seen passing over a normal-appearing antrum. Just proximal to the angulus of the greater curvature, an ulceration, sharply punched out and measuring 1.5 cm. in diameter, was noted. The margin was sharp and surrounded for a distance of 2 cm. by a flat, plateau-like area in which no rugae were present. The lesser curvature, from a distance of about 2 cm. above the ulcer down to the pylorus, was rigid and shortened. Not enough barium passed into the duodenum to fill out the duodenal bulb to normal contour. No barium left the stomach by way of any anastomosis.

A fasting gastric aspiration failed to produce free acid, but free acid was present after histamine. The patient was kept virtually pain free by hourly feedings. The temperature and white-cell count fell to normal. The morning gastric residual fluid was reduced from 300 to 75 cc. during the first week. On the seventeenth day, gastroscopy revealed a constantly deformed and rigid-appearing angulus. Its outline was irregular and slightly nodular. No peristalsis was visible. The ulceration seen at fluoroscopy was out of the range of the gastroscope.

Three days later, an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. CLAUDE E. WELCH*: We may as well start by seeing the x-ray films to get all the data.

*Associate visiting surgeon, Massachusetts General Hospital.

DR. RICHARD SCHATZKI: In addition to what is reported in the record I think I see something else that might be of significance. It seems to me that in these three films the lesser curvature is stiff over an area 5 cm. in length. The crater may be seen in profile in this film. In this next film the crater cannot be seen because there is too much barium. This stiffness, which I assume to be present, is the ulcer. There is marked swelling around the ulcer.

DR. ALFRED KRANES: Are you able to tell that the wall is stiff without fluoroscoping the patient?

DR. SCHATZKI: I certainly prefer fluoroscopy. On the other hand several films may allow some judgment. The normal stomach changes constantly in shape, and an area that does not change is usually rigid. We have not many films here, and I would like to have my hands on the patient's stomach.

DR. WELCH: I do not know what disease this patient had, but, as an academic exercise, we shall recount the methods of differentiating benign and malignant ulcer. In the first place, patients in the older age group who have a long story of gastric distress are more likely to have benign than malignant lesions. The patient with a short history is rather likely to have cancer. On this basis, we are slightly inclined toward ulcer in this case. The position of the ulcer is of importance. Almost all ulcers on the greater curvature are malignant. Those on the anterior or posterior walls carry about a 20 per cent chance of malignancy according to our figures in this hospital. Since this ulcer was on the posterior wall close to the greater curvature, the diagnosis is indeterminate from that criterion. The determination of free hydrochloric acid is not of great importance. If it is absent, one is inclined toward a diagnosis of a malignant lesion; but if free acid is present, cancer cannot be excluded.

Another method of differentiation is by the rate of healing. No evidence is offered in this case since the patient was observed in the hospital for only eight days. Another method is afforded by the type of pain, but, in this patient, who had a deeply penetrating lesion of the pancreas with tenderness in the epigastrium, pain is sure to have been present regardless of the diagnosis of ulcer or cancer.

A final bit of evidence is offered by the cytologic smear of the gastric contents. If the specimen obtained is in good condition and cancer cells are not seen, the differential diagnosis is still dubious because about a third of the carcinomas of the stomach do not shed cells. However, if cancer cells are reported from our laboratory, the chances of error are almost zero.

Whether or not such an examination was made is not mentioned in the protocol.

There is some additional evidence that this patient had ulcer rather than cancer. He had no weight loss in spite of the fact that the lesion was large. Also, examinations for occult blood in the stool were negative, and carcinoma is more likely to demonstrate this type of blood loss than is benign ulcer. The gastroscopic examination introduces a rather disturbing feature in that no peristalsis was observed around the margin. This is uncommon for ulcer and more typical of cancer, but in this particular patient, we have an element of pancreatitis superimposed because this lesion had perforated into the pancreas.

Considering all these features, the evidence is in favor of benign ulcer in this patient. The evidence is also strongly in favor of operation. An operation designed for cancer rather than an operation for benign lesion should be carried out.

DR. WALTER BAUER: I am trying to get Dr. Kranes to bet on the possibility that this was not benign. I want to bet that it is benign.

DR. SCHATZKI: I do not like to bet in a case like this because I think the evidence is not conclusive. If I were to take a chance, I would say cancer.

DR. MILFORD SCHULZ: It is not a deeply penetrating ulcer. Considering that ulcer occurs following necrosis in a spindle-cell tumor, would Dr. Schatzki like to say something about that and why he does not think it is one of that type?

DR. BENJAMIN CASTLEMAN: You mean an intramural extramucosal tumor?

DR. SCHULZ: Yes.

DR. SCHATZKI: From the evidence I would rather say no, but probably that is just what it is going to turn out to be. May I say one word about a statement Dr. Welch made: that an ulcer on the greater curvature is almost always malignant. I think that statement is based on surgical statistics, and roentgenologic statistics vary a bit because it depends on what one calls an ulcer of the greater curvature in one's statistics. In cases with any kind of ulceration of the greater curvature, there is an overwhelming number of cancers. If those that are grossly malignant are excluded and only the grossly benign lesions considered, the percentage of benign ulcers will go way up. I remember at least 3 or 4 ulcers of the greater curvature in this hospital that turned out to be benign. Statistics will vary among hospitals. In an active hospital the number of benign cases will go up because many more benign lesions will be operated on; it also depends considerably on the x-ray interpretation.

DR. CHARLES MIXTER, JR.: A cytologic smear was made, but it was unsatisfactory. At the time of operation the lesion was grossly benign. It was close to the greater curvature and appeared to invade the pancreas and transverse mesocolon. In view of the position of the lesion and because of apparent invasiveness we treated it as carcinoma and therefore elected to take out the tail of the pancreas and also a part of the transverse colon.

Clinical Diagnosis

Gastric ulcer.

Dr. Welch's Diagnosis

Benign gastric ulcer.

Anatomical Diagnosis

Benign gastric ulcer, greater curvature.

Pathological Discussion

Dr. Castleman: On the posterior surface along the greater curvature, 9 cm. from the proximal resection edge, was a perforated ulcer, partly walled off by the adjacent mesocolon, omentum and pancreas. When the stomach was opened the lesion was sharply punched out, and its grossly benign appearance was confirmed microscopically.

CASE 35462

Presentation of Case

First admission. A fifty-seven-year-old housewife was admitted to the hospital because of vomiting and a spontaneous black eye.

She was apparently well until four weeks before entry, when she developed a severe lumbosacral pain radiating at times to the left leg, not relieved by strapping and continuing intermittently until she entered the hospital. She also noted blood in the stool as well as some blood on the nightgown. Three weeks prior to admission she entered a community hospital for vaginal bleeding, the first since her menopause ten years previously. No diagnosis was made, and she was discharged after three days. One week before entry a rash appeared on the medial aspects of both legs and thighs. Four days before admission she developed mild vomiting and anorexia. There was no blood or bile in the vomitus.

The past history revealed an episode of pain in the right upper quadrant, with vomiting and jaundice, two years prior to admission. A cholecystostomy was performed, with the removal of several gallstones. The patient had been known to have mild diabetes for an indefinite period.

Physical examination revealed a well developed, moderately obese woman who was not acutely ill. There was a fading, papular rash over both posterior thighs and lateral aspects of the knees. There were right periorbital and scleral areas of ecchymosis. The lungs were clear. The heart was slightly enlarged to the left, and a Grade II, harsh systolic murmur was audible at the apex. Abdominal examination showed slight diffuse tenderness referred to the upper quadrant and some tenderness in both costovertebral angles. Pelvic and rectal examinations were negative. Examination of the fundi showed a few flame-shaped hemorrhages, with arteriolar narrowing and blurring of the disk margins, without papilledema. There was a questionable slight left facial weakness. Tendon reflexes were hypoactive throughout, but there was no asymmetry. Ankle jerks were absent bilaterally. Both plantar responses were down or absent. There was no weakness of the extremities. Sensation was intact; co-ordination was accurate.

The blood pressure was 140 systolic, 95 diastolic. The pulse was 85, and the respirations 20.

Urinalysis revealed a specific gravity of 1.020, a ++ test for albumin and intermittent green in the sugar reactions. A catheterized specimen showed 30 white cells per high-power field but no red cells or casts in the sediment. There was no bile or Bence-Jones protein. Examination of the blood revealed an initial hemoglobin of 11 gm. slowly falling to 8 gm. The white-cell count was within normal range; the platelets were adequate. Repeated determinations of the clotting time, prothrombin time, capillary fragility, bleeding time and platelet counts were within normal limits, as were the serum nonprotein nitrogen, the carbon dioxide combining power, the total protein, the calcium, the phosphorus, the amylase, the cholesterol and the cholesterol esters. The blood sugar ranged between 200 and 250 mg. per 100 cc. The bromsulfalein test showed 36 per cent retention of the dye in forty-five minutes. The van den Bergh reaction rose from normal to 1.6 mg. per 100 cc. The urine urobilinogen was 1.2 Ehrlich units in two hours. The thymol-turbidity and the cephalin-flocculation tests were negative. A blood culture was negative. An electrocardiogram revealed changes consistent with coronary-artery disease. An electroencephalogram was within normal limits. X-ray films of the chest were unremarkable except for some strand-like increase in density. Films of the spine, ribs, pelvis, hips and shoulders showed peculiar scattered areas of bone density. The second lumbar vertebra was denser than normal. Skull films were normal. A gastrointestinal series revealed no abnormalities. An intravenous pyelogram was normal except for a double pelvis in the right kidney. A bone-marrow aspiration showed marked stimulation of red-cell production. A vaginal smear was negative for tumor cells. A lumbar puncture revealed an initial spinal-fluid pressure equivalent to 400 mm. of water, falling after fifteen minutes, relaxation to 300 mm. Three cubic centimeters of clear spinal fluid was removed; the total protein was 104 mg. per 100 cc.; no cells were present.

During the two-week period in the hospital the vomiting cleared, and the ecchymoses of the skin and the right orbit faded somewhat. No new symptoms appeared. The diabetes was mild and was controlled without insulin. It was decided to observe the patient rather than to perform a craniotomy because of the symptoms of increased intra-

cranial pressure. On the fifteenth hospital day she was sent home to be followed in the Out Patient Department.

Final admission (six days later). After a very short stay at home the patient was readmitted because of increasing back pain and recurrence of the vomiting.

The neurologic examination remained unchanged. The fundi, however, revealed advanced papilledema and recent hemorrhages. Sensory changes were equivocal. Her mental state, which had been extremely poor, was unchanged.

On the fifth hospital day bilateral anterior temporal burr holes were made to rule out subdural hematoma. The right side revealed a thickened dura but no subdural fluid. Bleeding during the procedure was very profuse and difficult to control. On the following day she had a left hemiparesis of the face and upper extremity. Re-exploration revealed a recent operative blood clot in the right frontal burr hole. After enlargement of the incision no subdural accumulation of fluid was discovered. Dural and bone bleeding was controlled, but during the evening after operation oozing was noted over the bandage. Gradually, the patient became more comatose, and the blood sugar ranged from 350 to 450 mg. per 100 cc. On the eighth hospital day a right subtemporal decompression was performed because of jerking movements of the left arm and hand, suggesting possible subdural hematoma; but none was found. A repeated x-ray film of the chest showed an increased number of nodular densities.

During the following days the patient progressively deteriorated. She became very pale, the blood pressure dropped, and she died on the twentieth hospital day.

Differential Diagnosis

Dr. Victor G. Balboni*: We are dealing with a woman in late middle age who a month before entry developed severe back pain. At about the same time, she had vaginal bleeding and then vomiting, for which she was admitted to the hospital. She was found to have ecchymoses about the eye, and a rash, which may have been a purpuric rash although the record is not clear on that. The vaginal bleeding, the rash, the ecchymoses about the eye and the fact that later on she developed signs of an intracranial lesion raise the question of whether she had some form of bleeding tendency or purpura. However, the bleeding time, the clotting time, the prothrombin time and the tourniquet test were all within normal limits. Therefore it seems untenable to entertain seriously a diagnosis of purpura to account for the clinical course of this patient. The leg rash, I cannot explain. The ecchymoses about the eye, I think, may be explained on the basis of rupture of normal or slightly arteriosclerotic vessels while she was vomiting for four days. She had mild diabetes and was entitled to some vascular disease.

Vaginal bleeding is a much more important symptom, and in any woman of this age means cancer of the genital tract until proved otherwise. Pelvic and rectal examinations were negative. We are told that she had a previous hospital entry for three days, and I wonder if dilatation and curettage were done at that time. It would seem like a logical thing to do on a woman who was bleeding, but we have no information about that. A functioning ovarian tumor, a granulosa-cell tumor, may cause resumption of vaginal bleeding any time after the menopause, but granulosa-cell tumors are rarely malignant. Later on there is evidence that she had a malignant tumor with widespread metastases. Granulosa-cell tumors can become malignant and metastasize, but usually they do not. The vaginal smear showed no evidence of cancer cells. That is fairly good evidence against a malignant lesion of the uterus. It does not completely rule it out, however. Sometimes in reports of vaginal smears, the presence or absence of an estrogen effect in the cells is noted. I wonder if it was in this case.

Dr. John W. Littlefield: Yes, there was a marked estrogen effect in the smears.

Dr. Balboni: That raises another question. A not uncommon cause for vaginal bleeding in a woman of this age is oral or parenteral estrogenic medication.

A Physician: There was no history that she had been taking estrogenic medication.

Dr. Balboni: The fact that she showed an estrogen effect in the vaginal smear indicates that she had been taking estrogenic substances or that she had a functioning tumor of the ovary—a tumor making estrogen.

Later in the clinical course signs of increasing intracranial pressure developed, and the questionable right facial paralysis she showed on entry became very definite. In other words, she apparently had a lesion within the skull, and it probably was getting larger. The x-ray films show lesions in many of the bones and in the lung and from the description I gather that they were osteoblastic metastases. We might well review the films now.

Dr. James J. McCort: On the intravenous pyelogram a double kidney is seen on the right side. The liver edge is lower than normal. A study of the gastrointestinal tract discloses a normal esophagus, stomach and duodenum. No widening of the duodenal loop is seen. The colon was examined on two occasions and shows no intrinsic abnormality. On the films made of the colon it is noted that there are small densities present throughout the bones of the lower ribs, the lumbar spine and the pelvis. These densities are irregular and of varying size, extending up to 2 cm. in diameter. There is also increased density of the second lumbar

*Assistant in medicine, Massachusetts General Hospital.

vertebra, and I believe there is an area of destruction in the margin of the second lumbar vertebra with slight compression of the body of this vertebra. Small radiolucent areas are seen in the lower ribs. Examination of the chest, made on the first admission, shows a strand-like increase of density throughout both lung fields and small nodules in the peripheral lung fields. A film made on the second admission shows only a slight increase in the strand-like and nodular densities in both lung fields.

The films of the skull show one or two small radiolucent areas over the vertex having the appearance of venous lakes. The density extending across the parietal bones is due to a braid of hair. The sella turcica is normal in size and smooth in contour. There is no evidence of lesions in the skull. The calcified pineal body is in the midline.

DR. BALBONI: Is there anything abnormal about the duodenum? There is no widening?

DR. MCCORT: There is no widening and no evidence of intrinsic involvement of the duodenal wall. The liver, as I mentioned previously, seems somewhat larger than normal.

DR. BALBONI: Are the kidneys normal?

DR. MCCORT: Yes; the double kidney on the right is of no pathological significance.

DR. BALBONI: It is rare but not impossible for metastases from a single tumor to be both osteoblastic and osteolytic. Is that the situation here?

DR. MCCORT: The changes in the bone are both osteoblastic and osteolytic.

DR. BALBONI: With the help of the x-ray studies, the picture seems to be clearing a little bit. She had an x-ray picture of metastatic cancer, widespread throughout the skeleton, of both osteoblastic and osteolytic lesions and also lesions in the lung. The liver, which was not enlarged clinically, was slightly enlarged by x-ray study. There was abnormal function of the liver as manifested by the bromsulfalein retention. This was the only liver-function test that was abnormal, and it is consistent with involvement of the liver by tumor. I assume that part of the liver was destroyed by metastases but that the remaining liver cells were functioning normally and capable of performing all functions of the liver except excretion, which was somewhat reduced as evidenced by the bromsulfalein test and the van den Bergh reaction, which rose to 1.6 mg. per 100 cc.

The common tumors that metastasize to bone are: tumors of the breast, the prostate, the kidney and the bronchus. The only one I am sure was not involved here was the prostate, but there is little to suggest any of the others. The question of multiple myeloma in the bone, spreading widely through the pelvis, ribs and spine, has to be considered when one is confronted with lesions of this multiplicity, but such lesions are almost invariably osteolytic. Furthermore, at this stage of the game in multiple myeloma one would expect an elevated serum protein, and sometimes an elevated serum calcium. The absence of Bence-Jones protein in the urine is not against the diagnosis because it only occurs in about 50 per cent of cases of multiple myeloma.

Osteoblastic lesions are usually very slowly growing lesions such as may be seen in tumors of the pancreas. It is difficult to locate the primary site of the cancer. We know that she had previous gall-bladder disease, and she could have had a malignant lesion that developed in the gall bladder. Usually, in that situation, a mass is palpable in the region of the gall bladder. This woman apparently had none. I cannot locate the source of the tumor but I think she died of metastatic tumor involving the brain, the spine, the pelvis, the lungs and the liver. It would be unusual to have this a granulosa-cell tumor of the ovary that became malignant and spread, but in view of the fact that she had vaginal bleeding and an estrogen effect in the vaginal smear and in view of the fact that she had not taken any estrogen orally that diagnosis has to be considered. I would also seriously consider the gall bladder and pancreas as the primary site for the cancer.

A PHYSICIAN: Is the elevated blood sugar significant?

DR. BALBONI: She was known to have diabetes for a good many years, and I would think that the elevated sugar was consistent with her diabetes, which was aggravated by the surgical procedures she was subjected to.

DR. GREENE FITZHUGH: The diagnosis on the Medical Service was metastatic cancer. Our opinion was that we should biopsy that mass in the pelvis before having a neurosurgeon see her because of the brain lesions, but she got worse so rapidly that we transferred her to the neurosurgeons in the hope that they might be able to prolong her life.

CLINICAL DIAGNOSES

Disseminated neoplastic disease, unidentified.
Metastatic carcinoma of brain and lung.
Diabetes mellitus.

DR. BALBONI'S DIAGNOSES

Metastatic cancer involving brain, spine, pelvis, lungs and liver.
? Granulosa-cell cancer of ovary, ? cancer of gall bladder, ? cancer of pancreas.

ANATOMICAL DIAGNOSES

Carcinoma of gall bladder, with extension to extrahepatic bile ducts and peripancreatic nodes, and metastases to lungs and bones.
Cholelithiasis, with obstruction of ampulla of Vater.
Arteriosclerosis, generalized.

Operative scars: cholecystostomy, old; frontal burr holes, recent; subtemporal decompression, recent.

Pathological Discussion

Dr. Tracy B. Mallory: Autopsy on this patient disclosed a small, extremely firm, shrunken gall bladder, with thickened walls and some palpable excrescences of the mucosa. There was obvious tumor tissue extending down the length of the common duct, surrounding it completely, and extending into the region of the head of the pancreas. It was the impression, however, that the tumor nodules were lymph nodes around the head of the pancreas rather than in the pancreatic tissue and that the probabilities were all in favor of a primary carcinoma of the gall bladder that had spread to the pancreas rather than in the reverse direction. It is frequently very difficult to decide in this group of tumors which spot is primary. The tumor, extraordinarily enough, had not infiltrated the liver although it was in the lymphatics of the gall-bladder wall. Usually, carcinoma of the gall bladder invades the liver very widely and very early. In the lung the lesions were so small that they could not be picked up grossly, but microscopically the lymphatics throughout the pulmonary tissue were filled with tumor emboli.

One of the very unusual findings of the case was an obvious polyp of the endometrium, which on microscopical section showed metastatic cancer in the lymphatics within the polyp. The explanation of the central-nervous-system symptoms remains rather doubtful. I have to ask Dr. Kubik to tell us what he found.

Dr. Charles S. Kubik: No explanation for the cerebral symptoms has been found. Both explorations were negative for subdural hematoma, and at the second operation the brain itself was explored, with a negative result. On post-mortem examination there were numerous ecchymoses and small extravasations of blood on the inner surface of the dura, not only near the sites of the operations but also at considerable distances from them. This is almost surely a late development, which did not account for the cerebral symptoms. The conditions were probably explained by the surgical procedures and also perhaps by a hemorrhagic tendency, for which there was considerable clinical evidence, in spite of the negative blood studies. The patient did have ecchymoses of the skin and probably a hematoma of the orbit. There was little or no flattening of the convolutions, the ventricles were not enlarged, and there were no pressure cones. Aside from the mental status, papilledema, a spinal-fluid pressure equivalent to 400 mm. of water and a protein of over 100 mg. per 100 cc. were very real abnormal findings, and it is remarkable that nothing was found to explain them.

Dr. Mallory: I neglected to mention one finding that may have had some significance. There was embedded in the ampulla of Vater a small gallstone, so that she had definite cause for obstruction in the biliary tract — two causes, both carcinoma and the gallstone. In a certain number of cases of liver disease, this type of bleeding is seen when platelets, prothrombin time and everything else are normal; nevertheless, the patient bleeds extensively.

Dr. Alfred Kranes: She did not have liver disease?

Dr. Mallory: She had extrahepatic biliary-tract disease of severe grade without, however, clinical jaundice. The liver showed only insignificant changes.

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THANKSGIVING

That historic Thanksgiving in Plymouth Bay Colony, before the gobbling of turkeys was heard through the land, and when only a few handfuls of parched corn were available for the feast, has been succeeded by an era of plenty — at least for the prosperous.

Thanksgiving has not been the expression of a universal emotion, however, This country, even if less sharply than others, is also divided between the haves and the have nots, and many of the haves, apprehensive lest they lose what they hold, or discontented by nature, seem to find little enough for which to be thankful.

Thankfulness results from an appreciation of comparative values. On this basis nearly everyone has something to be thankful for, particularly in America. Most Americans, if they are not utterly derelict, can be thankful for enough to eat and a place to sleep. They can be thankful for freedom of speech under most circumstances, for freedom of action if it does not offend the majority or more powerful interests, and for freedom in selecting the type of medical care that is most suited to their needs.

They can be thankful for freedom to worship—to a less degree for freedom from religious intolerance. They can be thankful for many liberties, although all of them must be constantly protected against the inroads of bureaucracy. They can be thankful for the preservation, to date, of free enterprise, and for having been spared such reigns of terror as have become the lot of many other countries of the world.

BANNER WITH A STRANGE DEVICE

Among the activities associated with the United Nations the World Health Organization stands out as one of the most promising. Its program is reasonable and reminiscent of the good old days before 1914, when the civilized nations united in all sorts of mutually beneficial activities, such as uniform postal rates, copyright laws, weather reports, public-health regulations, the gold standard and hydrographic surveys, and global war had not been heard of since Waterloo except in the nightmares of H. G. Wells. If all nations could really agree on the importance of achieving world health, most other problems would be solved, for nothing is unhealthier than war and its sequelae.

Medical knowledge has kept pace with the technical advances that have marked a century of progress. This is what the chief of the American delegation to the second World Health Assembly, held in Rome from June 13 to July 2, may have had in mind when he declared in his report: "Unless we move forward to improve the health of mankind. . . it is impossible for mankind to move forward." The statement suggests a pleasing slogan: Gesundheit et excelsior! What might the nations accomplish if united under a banner with such a device!

Of course there is the risk that when mortal disease is abolished man will propagate so unrestrainedly that the world will be overpopulated in a few generations and that people will then die off, in

great batches, of suffocation and starvation. But this is not a serious threat at the moment.

The report referred to above points out that in the war-torn countries nonmilitary deaths per thousand have dropped in France from 15.2 in 1937–1939 to 10.5 in 1948, in Austria from 14.2 to 11.8 and in Japan from 17.3 to 12.0 (30 per cent less than any death rate previously recorded), and that before 1946 the death rate from malaria in Ceylon was 20 to 22 per thousand — a thorough dusting with DDT brought it down to 14.3 per thousand.

From the long-range point of view it would be more realistic to include the military deaths and the mortality among displaced persons, and to take some account of the psychiatric, moral and spiritual casualties of the past decade, but perhaps these are not germane to the subject. It is hoped that the old saw may be trusted — that when all men have sound bodies, sound minds will result.

At any rate, one cannot but agree with the American chief delegate that the United States may well increase its contribution to WHO from five to seven millions of dollars.

SHALL THE LADIES JOIN US?

Men, by and large, have one broad outlet for ministering to the health of their fellow beings. This is the profession of medicine, with its ramifications. Women, more subtly, have various methods of accomplishing the same purpose. The first, patently, is nursing, in which they reign supreme, casting into shadow men's efforts in this field. As medical secretaries, as technicians and in the research laboratory women perform subsidiary but invaluable services.

Other ways in which the more resourceful sex can contribute to the health of the community are illustrated by two interesting letters to the editor, to be found in this issue of the *Journal*. That from Dr. Edith Varney suggests the indomitable courage with which a young woman nearly sixty years ago, emulating Trotula, Rebecca and Constanza, the medical "ladies of Salerno," became one of the notable group of women physicians of this country.

The other, from the pen of the president of the Woman's Auxiliary to the Massachusetts Medical Society, gives intimations of the way in which women have guided the affairs of nations since the world began. As Esther to Ahasuerus, so may the women of the Auxiliary further the projects of their husbands and direct them into the most fruitful channels.

The Auxiliary is now a thousand strong; with the approval of its aims and the encouragement to join that will inevitably come to every wife from every husband in the Society, its enrollment should soon double and even triple. Fellows of the Society, however, must not wait for the moment when their wives will consult them on the desirability of membership, but urge them to join at once!

IT MIGHT HAPPEN HERE

The comparisons that have frequently been made between British Medicine under the National Health Service Act and what might happen in this country were similar circumstances to prevail can never be entirely to the point. Socialism in England is, at the moment, an accomplished fact. It is the result of conditions that have been long in the making. It is a system that has been accepted, however willingly or unwillingly, by a people whose traditions, social cleavages and economic problems are peculiarly their own.

It goes without saying that England's current system of medical practice is at present undesired in this country. The present Congress recognizes the fact, even as Congress, most of the medical profession and a majority of the people believe that improvement in the quality and distribution of medical care can and must and shall be made.

The British deserve credit for being among the most reasonable people on earth, with a wholesome respect for authority, once authority has been granted. Thus with Britain's minister of health, whose insistence on the acceptance of the present Health Act by Britain's medical profession caused so much unhappiness a year ago, Mr. Bevan's authoritative utterances on matters of health are now received unquestioningly, and duly appear in the British medical press.

In the section on Medical Notes in Parliament, in the *British Medical Journal* of August 6, 1949, following a request from Mr. Bevan that x-ray films be used economically, and a refusal by him to agree to a proposed transfer of the South-Western Hospital to St. Thomas's Hospital, there appears a decision from the minister regarding the toxicity of ducks' eggs. Ducks' eggs, according to this statement, are eaten most safely after being baked or fried or boiled for ten minutes provided they have not been preserved in water glass.

As an example of extreme co-operation on the part of the profession, the *Lancet* of May 28 refers to the hospital surgeon who wrote on a case paper: "This patient requires a hernia for his truss."

Among the 240 idiots described by the Commissioners to the Legislature of Massachusetts, 7 seem to have been made so by their mothers' trying to procure abortion by using very powerful drugs. Although these unborn children were not thus quite killed, yet they were irrecoverably stupefied and malformed to the lowest degrees of both mental and animal idiocy and weakness.

Boston M. & S. J., *November 14, 1849*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

SCHOLZ — Samuel B. Scholz, M.D., of Jenkintown, Pennsylvania, died on March 4. He was in his seventy-second year.

Dr. Scholz received his degree from Denver and Gross College of Medicine in 1905. He was medical director of the Penn Mutual Life Insurance Company of Philadelphia and was a fellow of the American College of Physicians and the American Medical Association and a retired member of the Massachusetts Medical Society.

His widow and a son survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

PROJECT FOR DENTAL RESEARCH

Under the provisions of Section 1, Chapter 473, of the *General Laws* of the Commonwealth, the Department has instituted a research project, which has been approved by the Massachusetts Dental Society, to evaluate the feasibility of expanding the training of auxiliary dental personnel. Under the law, the project is limited to a period of five years, the first two years being devoted to the training of female personnel and the last three representing an effort to determine the quantity and quality of dental service that can be rendered by auxiliary personnel to help overcome the wide disparity between dental needs and existing facilities. The project will be conducted at the Forsyth Dental Infirmary for Children. A representative group of students will be selected from the first-year class of the Forsyth School for Dental Hygienists, eventually to qualify as dental hygienists under the laws of Massachusetts.

Dr. Howard M. Marjerison and Dr. Charles E. Hatch, both members of the staff of the Infirmary, will be, respectively, director and clinical supervisor of the project. Dr. William D. Wellock, of the Dental Division of the Department, will act as liaison officer between the Department and the Infirmary, and Dr. William H. Griffin, dental director of the City of Boston Health Department and member of the State Health Department Public Health Council, is chief consultant. Other consultants appointed include leaders in dentistry and public health. In the near future, the commissioner, with the advice of the Massachusetts Dental Society and other interested groups, will appoint an advisory committee of dentists, public-health officers, social workers and other professional groups and civic leaders, to review periodically the reports of the project.

Every effort will be made to keep the dental profession informed of the progress of the project.

CORRESPONDENCE

NEVER UNDERESTIMATE THE POWER OF A WOMAN

To the Editor: The following two letters, which have been in my possession for many years, may prove of interest to the readers of the *Journal*, particularly as the first women to be admitted to Harvard Medical School are entering on their final year:

Harvard University,
Cambridge, September 22, 1890.

My dear Dr. Bowditch,—

I regret to say that there is as yet no provision for the medical education of women either in Harvard University or by the Society for Promoting the Collegiate Education of Women. Please excuse the delay in replying to your note of September 13th. It was first forwarded to Mount Desert and then returned to Cambridge.

Very truly yours,
Charles W. Eliot

Dr. Henry I. Bowditch.

Peterborough
Sept. 24, 1890

Miss Varney

Dear Madam:

I am not surprised at the tenor of President Eliot's reply, which I enclose. I deem the position of Harvard in regard (to) the education of women, one of which *eventually* the University will be *thoroughly ashamed*.

Even the word "Annex," which is connected with the Academic Department shows its low estimate of women. I never can think of it save with a certain contempt for the proud self-sufficiency evinced by the term. The Corporation virtually says "You women shall not join in the

Academic Rule because you are inferior to us; but as you want to learn something, we will have a small center connected with our University; an "Annex" and the professors, who choose to do so, are allowed to teach you in certain departments. But in this Department of Medicine in certain courses of which woman is fitter than man to practise the art — we will never teach you.

Thank Heaven! other Universities in this country and in Europe have higher ideals in regard to women.

I regret that I cannot help you, but if you think (of) any further counsel I can give you I hope you will write again.

Respectfully yours,
Henry I. Bowditch

Boston University took me in, from which I graduated in the Class of 1893. I interned at what is now Massachusetts Memorial Hospitals from January 1894 to 1895, then went abroad and spent a year studying at Vienna and other medical centers. I practiced in Lynn for fifty years, retiring four years ago.

EDITH C. VARNEY, M.D.

Newfields, New Hampshire

ORGANIZED HELPMATES

To the Editor: A well known physician telephoned me recently to solicit aid from the Woman's Auxiliary to the Massachusetts Medical Society in a particular matter. As a result of the conversation I was sure that this doctor had no idea who made up the membership of the Auxiliary, and what its objectives are.

Perhaps other *Journal* readers are unaware that there has been a national organization of doctors' wives since 1922, and that this society grew from a small reception to physicians' wives at the home of Dr. McReynolds of Dallas, Texas. In 1917 while Mrs. McReynolds was greeting a guest she asked her how she liked Dallas. The guest replied "I like Dallas very much. I have lived here for thirty years."

The wife or widow of any fellow in good standing in the Massachusetts Medical Society, who is not herself a physician and a fellow, is eligible for membership in her own district. We have a comprehensive twenty-point program and hope, with the help of our medical advisers, to have the whole state fully organized by 1950. Massachusetts has been far behind the other states in forming an auxiliary, but in our first year, under the leadership of Mrs. Leighton Johnson, we acquired a thousand members.

My message to the fellows of the Massachusetts Medical Society is: "Doctor, does your wife belong?"

ELIZABETH C. AYERS, *President*
Woman's Auxiliary to the
Massachusetts Medical Society

Worcester, Massachusetts

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The 1948 Year Book of Endocrinology, Metabolism and Nutrition. Endocrinology. Edited by Willard O. Thompson, M.D., clinical professor of medicine, University of Illinois College of Medicine, attending physician (senior staff), Henrotin Hospital, and attending physician, Grant Hospital of Chicago. *Metabolism and Nutrition.* Edited by Tom D. Spies, M.D., chairman, Department of Nutrition and Metabolism, Northwestern University School of Medicine, and director, Nutrition Clinic, Hillman Hospital, Birmingham, Alabama. 16°, cloth, 544 pp., with 87 illustrations. Chicago: Year Book Publishers, Incorporated, 1949. $4.50.

Contribución de la vitamina K a la terapéutica de la alergia. By Dr. E. F. Llovet. 12°, paper, 85 pp. Montevideo: Editorial "Montevideo," 1949.

Haematologica: Archivio. Vol. 32, 1948. 8°, paper, 508 pp. Pavia: Tip. "La Bodoniana," 1948.

Le Trincee Cliniche Della Tonsillectomia. By Guido Calderoli. 8°, paper, 78 pp. Bergamo, Italy: F.LLI Carrara, 1948.

NOTICES

ANNOUNCEMENTS

Dr. Robert H. McCarter announces the opening of an office at 65 Bay State Road, Boston, for the practice of psychiatry.

Dr. Irving H. Steinberg announces the opening of his office for the practice of internal medicine at 146 Chestnut Street, Springfield.

NEW ENGLAND CONFERENCES ON ALLERGY AND RELATED SUBJECTS

A number of programs on allergy and related subjects, open without charge to all interested, is planned for the coming year. These are to be presented under the auspices of the Department of Medicine of Boston University School of Medicine; Courses for Graduates, Harvard Medical School; and the Postgraduate Division, Tufts College Medical School.

The first meeting will take place on Wednesday afternoon and evening, November 30. The afternoon program, consisting of the presentation and discussion of cases with special emphasis on the use of the antihistaminic drugs, will be held in the lower Out Patient Department amphitheater of the Massachusetts General Hospital, Fruit Street, Boston, from 3:00 to 5:00 o'clock.

The evening program will take place in the Sheraton Room of the Copley Plaza Hotel, Copley Square, Boston, at 8:30 o'clock. Dr. Earl R. Loew will speak on the subject "The Role of Histamine in Anaphylaxis and Allergy in the Light of Experience with the Antihistaminic Drugs."

All members of the medical profession are cordially invited to both the afternoon and the evening meetings.

NEW ENGLAND PEDIATRIC SOCIETY

The next meeting of the New England Pediatric Society will be held in Boston on Wednesday, December 7.

The afternoon and evening meeting will be devoted to a discussion of ACTH.

A detailed program will be published at a later date.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

The December and January meetings of the New England Society of Anesthesiologists will be as follows:

A regular meeting will be held in the Auditorium of Building A, Boston University School of Medicine, Boston, on Tuesday, December 13, at 8 p.m. Dr. Emanuel M. Papper, executive officer and professor, Department of Anesthesia, Columbia – Presbyterian Medical Center, New York City, will speak on the subject "Diagnostic and Therapeutic Nerve Blocks."

A regular meeting will be held in the Auditorium of Building A, Boston University School of Medicine, Boston, on Tuesday, January 10, at 8 p.m. Dr. Edward F. Bland will speak on the subject "The Appraisal and Preparation of Poor Risk Patients for Surgery."

94TH INFANTRY DIVISION LECTURES

The 94th (Bay State) Infantry Division is sponsoring a series of monthly lectures by prominent physicians in their respective specialties. The ninth lecture will be held in the auditorium of Boston University School of Medicine, 80 East Concord Street, Boston, on Thursday, December 15, at 8 p.m.

Dr. Eugene R. Sullivan will speak on the subject "Crush Syndrome and Related Conditions."

All interested physicians, whether reserve officers or not, are cordially invited to attend this carefully planned program. Reserve officers will be given one point credit if authorized by the instructor of their unit of assignment. Excellent films will be shown during this period.

(*Notices concluded on page xv*)